Journal of
Pharmacology & Clinical Research
ISSN: 2473-5574

Juniper Publishers
key to the Researchers

Research Article
Volume 5 Issue 3 - April 2018
DOI: 10.19080/JPCR.2018.05.555664

J of Pharmacol & Clin Res


# Effect of Galantamine with Neuropharmacological Benefits in Wistar Rats Models of Epilepsy and Behaviour

**Nidhi Tyagi*, Radha Goel, Mohd Junaid, Ravi Kumar Saini and Veerbala Singh**

*School of Pharmaceutical science, Shri Venkateshwara University Gajraula UP, India*

**Submission:** March 05, 2018; **Published:** April 27, 2018

***Corresponding author:** Nidhi Tyagi, School of Pharmaceutical science, Shri Venkateshwara University Gajraula UP, India, Email: nidhityagi94pharmacist@gmail.com

**Abstract**

Involvements of oxidative damage, deficiency of acetylcholine and cognitive impairment have been reported in the Pathophysiology of epilepsy. It has been demonstrated that cholinesterase is degranulated at the site of a lesion it cause brain disorder leading to epilepsy. Cholinesterase inhibitor (Galantamine) inhibits the release of cholinesterase thus it benefits in epilepsy. So the aim of the study was to evaluate both effect cholinesterase inhibitor (Galantamine) and cognitive behaviour in epilepsy induced by increasing Current Electroshock Seizures test of wistar rats. Epilepsy was evaluated by behavioural tests such as Spontaneous alternation behaviour and rota road test. Measurement of oxidative stress was done by various biochemical estimations namely Lipid peroxides (in brain), Protein estimation using Folin's reagent and Brain reduced glutathione estimation. All the results 0f Galantamine (0.5mg/kg and 1mg/kg) were compared to the standard drug sodium valporate (100mg/kg and 200mg/kg).

**Abbreviations:** Spontaneous alternation behaviour; Galantamine; Sodium valporate; Epilepsy

## Introduction

Epilepsy is a disorder of the central nervous system characterized by periodic loss of consciousness with or without convulsions associated with abnormal electrical activity in the brain. In some cases it is due to brain damage, but in most cases the cause is unknown [1]. Epileptic seizures typically involve excessive firing and synchronization of neurons. This interrupts the normal working of the parts of the brain involved, leading to the clinical symptoms and semiology of the specific type of epilepsy. This chapter will outline basic mechanisms of epileptic discharges, particularly in terms of the cellular electrophysiology of focal epilepsies. It will outline recent advances in clarifying the concept of 'hyper synchronous' neuronal activity during seizures [2]. There are 50 million people living with epilepsy worldwide, and most of them reside in developing countries. About 10 million persons with epilepsy are there in India. Many people with active epilepsy do not receive appropriate treatment for their condition, leading to large treatment gap. The lack of knowledge of antiepileptic drugs, poverty, cultural beliefs, stigma, poor health infrastructure, and shortage of trained professionals contribute for the treatment gap. Infectious diseases play an important role in seizures and long-term burden causing both new-onset epilepsy and status epilepticus. Proper education and appropriate health care services can make tremendous change in a country like India [3]. A provoked seizure would include traumatic injuries to the head, whereas an unprovoked seizure would include seizures caused by, for example, a congenital defect [4]. Lack of Oxygen (Hypoxia) an insufficient supply of oxygen to the brain can cause seizures the skull offers a great deal of protection, these incidents seldom result in brain injury and subsequent epilepsy Infections of the Central Nervous System Brain infections can cause seizures during acute stages of the infection. Cancerous and benign brain tumors and other lesions can cause seizures. [5]. In rats right frontal cerebral cortex, acetylcholine (ACh) levels were depressed in the visually non-necotic, surrounding cortex at 7 and 14 days after surgery that cause epilepsy. And the rats treated with cholinesterase inhibitor (Galantamine) for epilepsy. The cholinesterase inhibitors, physostigmine and diisopropyl fluorophosphate reduced seizure activity in rats [6].

## Pharmacological Treatment of Epilepsy

### Sodium Channel Blockers

Sodium channel blocking is common and best-characterized mechanism of currently available antiepileptic drugs. AEDs that

target sodium channels prevent the return of the channels to the active state by stabilizing the inactive form. In doing so, prevent the repetitive firing of the axons [7].

**Phenytoin:** Phenytoin is the most common inexpensive AED, mostly general physicians are used Phenytoin. motor cortex is a primary site of action where spread of seizure activity is inhibited. Possibly neurons promoting sodium efflux, Phenytoin tends to stabilize the threshold against hyper-excitability caused by excessive stimulation or environmental changes capable of reducing membrane sodium gradient. Phenytoin reduces the maximal activity of brain stem centres responsible for the tonic phase of tonic clonic (grand mal) seizures. Adult recommended dose is around 300 mg/day. Unsteadiness and moderate cognitive problem these are common side effect [8].

**Carbamazepine:** Carbamazepine is a favourite partial seizure medicine in the developed world. Carbamazepine affects sodium channels, and inhibits rapid firing of brain cells. Long-acting forms such as Carbatrol or Tegretol-XR can be given once a day. Typical adult dose is 400 mg TID. Potential side effects include GI upset, weight gain, blurred vision, low blood counts, low blood sodium (hypo-natremia). Carbamazepine causes a rash rate of a few percent, sometimes even the dangerous rash called Stevens-Johnson syndrome. People of Asian descent with HLA-B*1502 antigen are more at risk [9].

**Oxcarbazepine:** Somewhat unique in relation to Carbamazepine, it is in any event as compelling, and may have less symptoms, with the exception of more hazard for low blood sodium (hyponatremia). Oxcarbazepine does not create the harmful 10,11epoxide metabolite, which is to a great extent in charge of the unfriendly impacts detailed with Carbamazepine. It is more costly than non specific Carbamazepine. A run of the mill grown-up dosage is 600 mg twice per day [10].

**Lamotrigine:** Lamotrigine is an expansive range other option to Valproic corrosive, with a superior symptom profile. Not with standing, LTG may not be as viable for myoclonic seizures. Lamotrigine works by a few instruments including s blocking voltage-subordinate sodium-channel conductance, blocking arrival of glutamate, the mind's primary excitatory neurotransmitter. It has the standard symptoms of wooziness and weakness, normally mellow intellectual (considering) hindrance. Serious medicinal reactions are unordinary. The commonsense symptom issue is impulsive, happening in 5-10% of individuals who take it, particularly if the dosage is expanded too quick [11].

**Zonisamide:** Zonisamide applies its system of activity by decrease of neuronal tedious terminating by blocking sodium channels and anticipating neurotransmitter discharge. It likewise applies impact on T-sort calcium channels and counteracts convergence of calcium. Likewise, ZNS shows neuroprotective impacts through free radical rummaging. It is fairly comparable in its scope and symptoms to Topiramate, aside from glaucoma is not generally recorded [12].

**Lacosamide:** Lacosamide is another (2009) antiepileptic medicate, for fractional and optionally summed up seizures. It is artificially identified with the amino corrosive, serine. They squares sodium channels (however uniquely in contrast to other seizure pharmaceuticals), and this piece lessens cerebrum volatility. Symptoms incorporate discombobulation, cerebral pain, queasiness or regurgitating, twofold vision, weariness, memory or inclination issues. It might influence the interior organs, blood tallies or heart musicality, yet these possibly genuine symptoms are rare [13].

**GABA Receptor Agonists:** A seizure mirrors an unevenness amongst excitatory and inhibitory action in the mind, with an addition of excitation over restraint. The most essential inhibitory neurotransmitter in the mind is gamma-aminobutyric corrosive (GABA). There is an intriguing connection between this most plentiful and essential inhibitory specialist (GABA) and glutamate, the motor of excitation. GABA-A receptors have numerous coupling destinations for benzodiazepines, barbiturates, and different substances (e.g., neurosteroids). These medications tie to various destinations around the receptor to apply their activity, yet the clinical ramifications of every receptor site are not surely knew. The benzodiazepines most usually utilized for treatment of epilepsy are lorazepam diazepam, midazolam, clonazepam, chlorazepate and clobazam [14].

**Phenobarbital:** Phenobarbital is a customary, exceptionally modest and viable in a solitary every day measurement. Phenobarbital builds the impact of GABA, the primary inhibitory neurotransmitter in the cerebrum. Phenobarbital is utilized for tonic-clonic and halfway seizures and may likewise be attempted in atypical nonattendance; atonic and tonic seizures. Phenobarbital is somewhat addictive and requires moderate withdrawal. Amid pregnancy, there is a critical rate of birth deformities [15].

**Clonazepam:** Clonazepam is an individual from the medication class known as benzodiazepines, to which diazepam, lorazepam, clorazepate, alprazolam likewise has a place. Benzodiazepines are utilized as hostile to seizure drugs, narcotics, sedatives and muscle relaxants. Benzodiazepines increment the adequacy of GABA, the cerebrum's primary inhibitory neurotransmitter. Clonazepam is more long-acting against seizures than are diazepam or lorazepam. Reactions of Clonazepam incorporate sedation, considering/memory weakness, state of mind changes, and habit [16].

**GABA Reuptake Inhibitors:** Reuptake of gamma-aminobutyric corrosive (GABA) is encouraged by no less than 4 particular GABA-4transporting aggravates; these convey GABA from the synaptic space into neurons and glial cells, where it is processed. Nipecotic corrosive and Tiagabine (TGB) are inhibitors of these transporters; this hindrance makes expanded measures of GABA accessible in the synaptic parted. GABA delays inhibitory postsynaptic possibilities (IPSPs) [17].


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**Tigabine:** Tiagabine is a «planner tranquilize», defined to piece inactivation (take-up) of the mind's primary inhibitory neurotransmitter, GABA. At the point when more GABA collects in the cerebrum, seizures are harder to start and manage. It is helpful for fractional and optionally summed up seizures. It is not compelling for nonappearance or myoclonic seizures [18].

**GABA Transaminase Inhibitors:** Gamma-aminobutyric acid (GABA) is metabolized by transamination in the extracellular compartment by GABA-transaminase (GABA-T). Inhibition of this enzymatic process leads to an increase in the extracellular concentration of GABA. Vigabatrin (VGB) inhibits the enzyme GABA-T [19].

**Vigabatrin:** Vigabatrin is a "designer drug," made to block metabolism of GABA, the brain's main inhibitory neurotransmitter. It is a close structural analogue of GABA, binding irreversibly to the active site of GABA-T. Vigabatrin has been used for over a decade in many countries, and it is effective for partial seizures, with or without secondary generalization. It also may be very effective for infantile spasms, a serious type of seizures in young children [20].

### Effect of Cholinesterase in Epilepsy

In rats right frontal cerebral cortex, acetylcholine (ACh) levels were depressed in the visually non-necotic, surrounding cortex at 7 and 14 days after surgery that cause epilepsy. And the rats treated with cholinesterase inhibitor. The cholinesterase inhibitors, physostigmine and diisopropylfluorophosphate reduced seizure activity in rats. Hemicholinium-3 (HC-3), given sub acutely initially inhibited seizures, but seizure frequency increased later during treatment [6].

### Epilepsy and Cognitive Behaviour

Cognitive dysfunction is one of the major contributors to the burden of epilepsy. It can significantly disrupt intellectual development in children and functional status and quality of life in adults. Epilepsy affects cognition through a number of mechanisms in complex interrelationship. Cognitive deficits in epilepsy may be treated indirectly through aggressive seizure control using anti-epileptic drugs or surgery, and by treating comorbid conditions such as depression. The beneficial effects of reducing seizures may offset the adverse cognitive side-effects of these therapies. Direct treatment of cognitive impairment in epilepsy mainly involves memory rehabilitation. Other direct treatments are mostly experimental and their evidence base is currently poor [21].

### Epilepsy and Oxidative Stress

Oxidative stress, a state of imbalance in the production of reactive oxygen species and nitrogen, is induced by a wide variety of factors. This biochemical state is associated with systemic diseases, and diseases affecting the central nervous system. Epilepsy is a chronic neurological disorder with refractoriness to drug therapy at about 30%. Currently, experimental evidence supports the involvement of oxidative stress in seizures, in the process of their generation, and in the mechanisms associated with refractoriness to drug therapy so it is cause epilepsy [22]. Galantamine has a unique, dual mode of action. It is a reversible, competitive inhibitor of acetylcholinesterase (AChE), and is the only drug actively marketed for the treatment of AD with proven activity as an allosteric modulator of nicotinic acetylcholine receptors (nAChRs) Galantamine have lipophilic in nature [23].

So, the aim of the study will evaluate the effect of anticholinesterase in epilepsy and find the beneficial effect of anticholinesterase on treatment epilepsy.

## Drug Profile

### Galantamine [24]

**Pharmacology:** Galantamine, a tertiary alkaloid, is a competitive and reversible inhibitor of acetyl cholinesterase. While the precise mechanism of galantamine's action is unknown, it is postulated to exert its therapeutic effect by enhancing cholinergic function. This is accomplished by increasing the concentration of acetylcholine through reversible inhibition of its hydrolysis by cholinesterase. Galantamine's effect may lessen as the disease process advances and fewer cholinergic neurons remain functionally intact (Table 1).

**Table 1**.

| | |
|---|---|
| Plasma Half Life | 7 hr |
| Bioavailability | 80 – 100% |
| Protein Binding | >18% bound to plasma protein |
| Site of Metabolism | Hepatic |
| Metabolites | CYP450:CYP2D6/3A4substrate |
| Excretion | Renal excretion |
| Peak plasma concentration | 1 hour |

**Adverse Effects:** Common adverse effects of Galantamine are nausea, vomiting, diarrhoes, abdominal discomfort, bradycardia, decreased appetite, depression.

**Therapeutic Uses:** Vascular dementia, Alzheimer disease.

### Sodium Valporate [25]

**Table 2.**

| | |
|---|---|
| Plasma Half Life | 9-16 hr |
| Bioavailability | 23% |
| Protein Binding | Concentration dependent |
| Site of Metabolism | Hepatic |
| Tmax | 2-3.5 hr |
| Excretion | Renal excretion |
| Peak plasma concentration | 90 min |

**Pharmacology:** Valproic acid dissociates to the valproate ion in the tract. Valporate has been shown to have anticonvulsant property in the variety of experimental models in epilepsy. It has also been shown to be effective in the treatment of epilepsy in man. Valporate increase the levels of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) at GABAA


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and GABAB receptors possibly resulting from the activation of the synthetic enzyme glutamic acid decarboxylase and inhibition of the catabolic enzyme succinic semialdehyde dehydrogynase and GABA transaminase . Valporate inhibits neuronal cell firing induced by NMDA (Table 2).

**Adverse Effects:** Nausea, vomiting, dizziness, rash.

**Theraputic Effect:** Epilepsy

## Objective of Study

a) The objective of the study is to evaluate the effect of Galantamine with neuropharmacological benefits in rodents models of epilepsy and behaviour.

b) To determine the behavioural and biochemical changes.

c) To assess the histopathological changes in the brain (hippocampus)

## Material and Methods

### Animals

All experiments were performed on adult wistar rats weighing 150-130 g. The animals were procured from the Animal House, I.T.S College of Pharmacy Muradnagar, Ghaziabad. Animals were housed in group of 6 per cages, maintained at 23_+20C; 55+_5% humidity in a natural lightand dark cycle, with free access to food and water. The experiments were performed during the light cycle in awake, freely moving animals that were adjusted to laboratory conditions before proceeding with the experiments. All animal procedures were approved by the ethical committee at our institution (CPCSEA registration number: 1044/c/07/CPCSEA) and performed in compliance with institutional guidelines for the care handling of experimental animals.

### Experimental Design

**Oral Administration of Drugs:** Drugs were suspended to desired concentration in CMC in saline and administered orally. Equivalent volumes of CMC in saline were given to control groups. All the drugs were given in volumes of 10 ml/kg.

**Dose:** Sodium valporate was administerd at a dose of 50 and 100 mg/kg [26]. Galantamine was administerd at a dose of 0.5, and 1 mg/kg [27]. The drug treatment was given for 21 days and observations was make at the 21$^{th}$ day after drugs treatment. The observations were made at the time of peak effect of the drugs . (for Galantamine after 1 hr, for SVP after 90 min).

**Experimental Protocol:** The experimental protocol was divided into following groups. In this experiment, the following groups of six mice each was administer drugs once daily for the duration of 21 days. All the groups would undergo all the parameters. At the end of each treatment the mice was euthanized for collection of brain tissue for biochemical estimations (Table 3).

**Table 3**

| Group | No. of Animals | Treatment | Dose (mg/kg) (p/o) | Duration |
|---|---|---|---|---|
| 1 | 6 | Control | Vehicle | 21 Days |
| 2 | 6 | Sodium valporate | 100mg/kg | 21 Days |
| 3 | 6 | Sodium valporate | 200mg/kg | 21 Days |
| 4 | 6 | Galantamine | 0.5mg/kg | 21 Days |
| 5 | 6 | Galantamine | 1mg/kg | 21 Days |
| 6 | 6 | Sodium valporate +Galantamine | 100mg/kg +0.5mg/kg | 21Days |
| 7 | 6 | Sodium valporate + Galantamine | 100mg/kg +1mg/kg | 21 Days |
| 8 | 6 | Sodium valporate + Galantamine | 200mg/kg +0.5mg/kg | 21 Days |
| 9 | 6 | Sodium valporate + Galantamine | 200mg/kg +1mg/kg | 21 Days |
| | 54 | | | |

### Parameters Assessed

The various parameters assessed during the study were as following:

#### Behavioural Estimation

**a) Spontaneous Alternation Behaviour (SAB):** Cognitive function was assessed by measuring percentage alternation on a plus-maze based on specification of and consisted of four arms (height: 50 cm; length: 23.5 cm; breadth: 8 cm; wall height: 10 cm) with a central platform (8×8 cm). The arms were labeled as A, B, C and D and percentage alternation was measured following the method of [28].

After being placed in the central platform, mice were allowed to move in the maze freely for 6 min. The number and sequence of entries were recorded. A 4/5 alternation was defined as entry into 4 different arms on overlapping quintuple sets. Five consecutive arm choices made up a quintuple set e.g. a quintuple set consisting of arm choices A, B, C, D, B was considered as an alternation, while A, D, C, D, A was not considered as quintuple. Using these procedures percentage alternation was calculated as follows:

$$\%Alternation = \frac{ActualNumberofAlternations}{PossibleAlternation} * 100$$

Where possible alternation = number of arm entries - 4.


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**b) Rotarod Test:** Effects on motor function were assessed by [29]. In this test a rod with a diameter of 3cm rotating at a constant speed of 6 rpm was used. The mice were placed on the rotating rod and the time taken to fall was noted.

**Biochemical Estimations**

**a) Lipid Peroxides (in brain) [30]:**

**i. Principle**

Lipid peroxidation is a free radical mediated event. The primary products of such damage are a complex mixture of peroxides which then breakdown to produce carbonyl compounds The malondialdehyde (MDA) is one such carbonyl which forms a characteristic chromogenic adduct with two molecules of thiobarbituric acid (TBA). The calorimetric reaction of TBA with MDA, a secondary product of lipid peroxidation has been widely adapted as method for measuring lipid peroxidation.

**ii. Reagents**

**a)** 0.8% thiobarbituric acid (TBA) solution: 80 g of TBA was dissolved in distilled water and the volume was made up to 100 ml.

**b)** 30% trichloroacetic acid (TCA) solution: 30 g of TCA was dissolved in distilled water and the volume was made up to 100 ml.

**c)** KCl solution: 2.42 g of KCl was dissolved in distilled water and the volume was made up to 100 ml.

**iii. Method**

One ml of suspension medium was taken from the 10% of tissue homogenate. 1 ml of 30% TCA was be added to it, followed by 1 ml of 0.8% TBA reagent. The tubes was covered with the aluminum foil and kept in a shaking water bath for 30 minutes at 80 degree centigrade. After 30 minutes, tubes was taken out and kept in ice-cold water for 30 min. These were then centrifuged at 3000 rpm for 15 minutes. The absorbance of the supernatant will be read at 535nm at room temperature against the appropriate blank. Blank consists of 1ml distilled water, 1ml of 30% TCA and 1ml of 0.8%TBA.

**iv. Calculation**

The content of MDA expressed as n moles formed per mg of protein in the tissue was calculated using the formula: -

$$Concentration = A*V / E*P$$

Where A is absorbance.

V is the vol. of solution.

E is extinction coffecient ($1.56*10^{-6}m^{-1}cm^{-1}$).

P is the protein content of tissue calculated as mg protein / gm.

**b) Protein Estimation Using Folin's Reagent [31]:**

**i. Principal**

Protein reacts with the folin's ciocalteau phenol reagent to give colored complex. The color so formed is due to reaction of alkaline copper with the protein as in the biurate test and the reduction of phosphomolybdate by tyrosine and tryptophan present in the protein.

**ii. Reagents Required**

**a)** Alkaline sodium carbonate solution: 100 ml of 0.1 N NaOH solution was prepared by dissolving 400 mg of NaOH in distilled water and the volume was made up to 100 ml . Then 2 g of $Na_2CO_3$ was dissolved in 100 ml of 0.1 ml NaOH.

**b)** Copper sulphate sodium tartrate solution: 500 mg of $CuSO_4$ was dissolved in 100 ml of distilled water and mixed it with 1000mg of Na-K tartarate which is dissolved in 100 ml of distilled water.

**c)** Alkaline solution prepared on the day of use by mixing 50ml of the reagent 1 and 1ml of reagent2

**d)** Folin's ciocalteau phenol reagent: The commercial reagent was diluted with 2 volumes of distilled water on the day of use.

**e)** Standard Protein: Bovine serum albumin solution (2mg/ml): - 10 ml of bovine serum albumin was dissolved in 5 ml distilled water to get a solution of 2mg/ml of protein.

**iii. Method**

5ml of alkaline solution was graded to 1 ml of suspension from the supernatant after centrifugation of the 10% tissue homogenate at 3000 rpm and allow to stand for 10 minutes. 0.5ml diluted folin's reagent was added and the tube will be shaken to mix the solution, after 30 minutes, the extinction against appropriate blank at 750 rpm will be recorded.

**iv. Preparation of Calibration Standard Curve of Protein**

5 ml of bovine albumin solution (2mg/ml) was prepared and different volumes will be taken in 6 tubes. To all tubes, distilled water will be added to make up the volume in each tube to 1 ml. The protein concentration in the above 6 tubes was estimated in the same way as for the sample. A graph was plotted between concentration of protein and optical density.

**c) Brain Reduced Glutathione Estimation [32]:** Glutathione in the tissue was estimated by the method of Sedlac and Lindsay (1968) using Ellman reagent.

**i. Reagents**

**a)** EDTA (0.2 M ): 22.3 gm of EDTA was dissolved in 300 ml of warm double distilled water.


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**b)** EDTA (0.02 M): 20 ml of above solution was diluted to 200 ml with double distilled water.

**c)** Tris buffer -0.4 M ( PH 8.9 ): 24.2 gms of tris buffer was dissolved in 100 ml of double distilled water . 50 ml of 0.2 M EDTA was added to it and the volume of the solution was made up to 500 ml with double distilled water. The PH of the solution was adjusted to 8.9 with ( 6N HCl )

**d)** DTNB (0.01 M): 99 mg of DTNB was dissolved in 25 ml of absolute methanol.

**e)** Tricholoro acetic acid (TCA 50%): 50 gm of TCA was dissolved in 100 ml of double distilled water.

**ii. Method**

Mice were sacrificed by instant decapitation. The brains were quickly removed and washed with ice cold saline. 2ml of 10% homogenate, which was prepared in KCl solution, were taken and add 2.5 ml of 0.02 M EDTA. Shake it vigorously. Take out 2ml of the above mixture and add 4ml of cold distilled water and 1 ml of 50% TCA and shake it for 10 minutes. . 10 minutes later the content was transferred to centrifuged tube and centrifuged at 300 rpm for 15 min. Following centrifugation, 2 ml of the supernatant was mixed with 4 ml of 0.4 M tris buffer (PH 8.9) .The whole solution was mixed well and 0.1 ml of 0.01 M DTNB was added, the absorbance was read with in 5 min . of addition of DTNB at 412 nm against reagent blank with no homogenate . For blank readings, instead of 2ml of homogenate 2ml of distilled water was added.

**iii. Calculation**

Total GSH (tissue) was calculated using the formula described by Ellman (1959). Thus the content 'C0' of GSH is given by

Co = A*D /E

Where A is absorbance at 412nm

D is dilution factor

E is the molar extinction coefficient (C= 13000M-1cm-1)

Co is the concentration of glutathione.

**Histological Examination**

**a) Behavioural Study:** Samples of brain was stored in the fixative solution (10% formalin) and cut into 4 µm thickness size. Staining was done by using haematoxylin and eosin as described by Yukari method. Nerve sections will be analyzed qualitatively under light microscope (450 ×) for axonal degeneration [33].

## Histopathological Study

Samples of brain was stored in the fixative solution (10% formalin) and cut into 4 µm thickness size. Staining was done by using haematoxylin and eosin as described by Yukari method. Nerve sections will be analyzed qualitatively under light microscope (450 ×) for axonal degeneration [33].

**Statistical Analysis:** All the results was expressed as mean ± standard deviation (SD) followed by analysis of variance (ANOVA) along with Dunnett comparison test. The $p<0.05$ will be considered to be statistically significant.

**Procedure of Brain Extract:** The rats were died with the procedure of survical dislocation and then upper side of the neck were shaved and the skin were sterilized with ethanol. All surgical instruments were sterilized before surgery. The upper neck of the rat is dissection is made to expose the brain inside the bone skull of brain. Put the brain from bone skull with the help of forshape and put into the formalin solution (Figure 1).

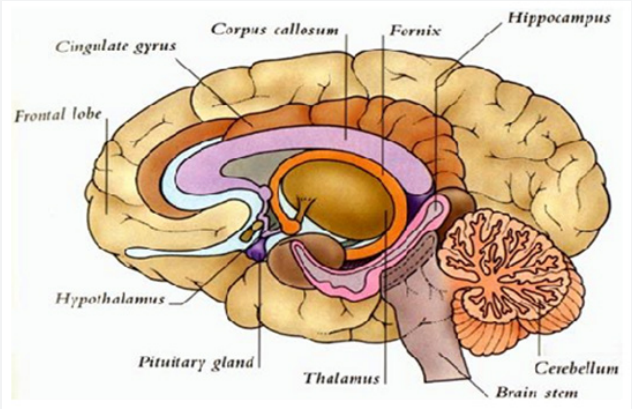


**Figure 1:** Hippocampus part in brain.

## Result

### Effect of Galantamine on ICES Model

The seizure threshold is increased significantly ($p<0.01$) when treated with alone as well as in combination of Galantamine with sodium valporate i.e. (100mg/kg SVP and 0.5mg/kg Galantamine, 100mg/kg SVP and 1mg/kg Galantamine ,200mg/kg SVP and 0.5mg/kg Galantamine ,200mg/kg SVP and 1mg/kg Galantamine) when compared to normal control group and sodium valporate at both the doses (Table 4) and (Figure 2).

**Table 4**: All values were expressed as mean ± S.E.M. (n=6), a= p<0.01 when compared with control group; b= p< 0.01 when compared to Sodium valporate, c=P<0.01 when compared to Sodium valporate(2000mg/kg )(ANOVA followed by Dunnett, s test).

| Groups | ICES MODEL |
|---|---|
| Group 1 (normal) | 13.16 ± 0.3073a |
| Group 2 (100mg/kg sodium valporate) | 18.66 ± 0.2108[a] |
| Group 3 (200mg/kg sodium valporate) | 20.5 ± 0.2236[a] |
| Group 4 (0.5mg/kg Galantamine) | 15.16 ± 0.3073[a] |
| Group 5(1mg/kg Galantamine) | 17.16 ± 0.3073[a] |
| Group 6(100mg SVP& 0.5mgGalantamine) | 22.16 ± 0.3073[a,b,c] |
| Group 7(100mg SVP& 1mgGalantamine) | 24.5 ± 0.2236[a,b,c] |
| Group 8(200mg SVP& 0.5mgGalantamine) | 26.5 ± 0.2236[a,b,c] |
| Group 9(200mg SVP& 1mgGalantamine) | 28.5 ± 0.2236[a,b,c] |


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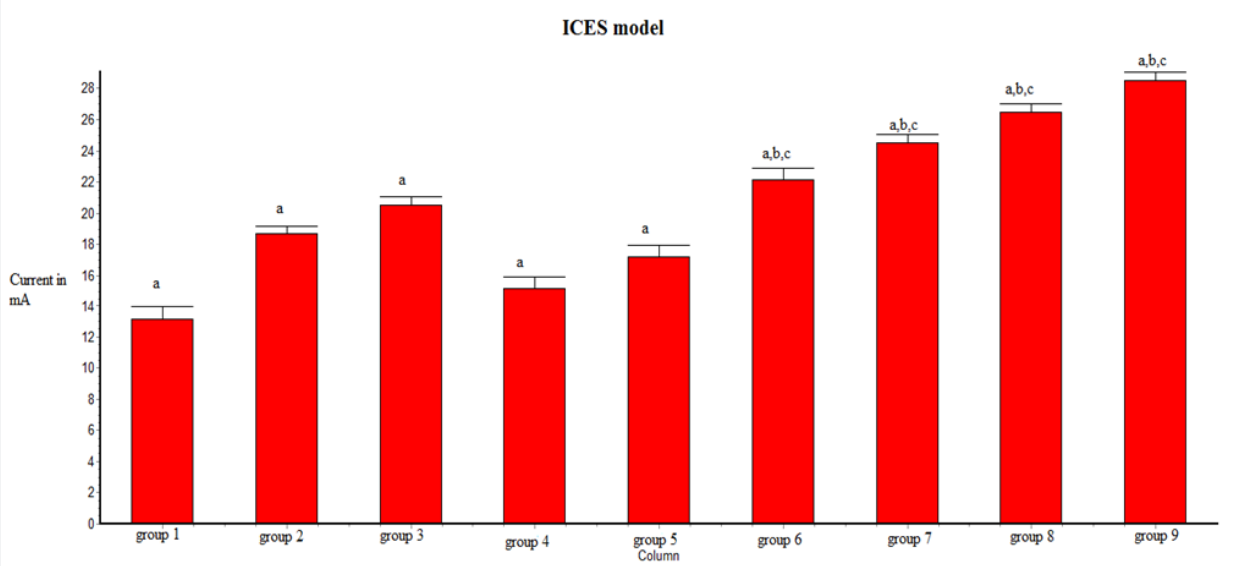


**Figure 2:** All values were expressed as mean ± S.E.M. (n=6), a= p<0.01 when compared with control group; b= p< 0.01 when compared to Sodium valporate, c=P<0.01 when compared to Sodium valporate(2000mg/kg) (ANOVA followed by Dunnett, s test).

## Behavioural Parameters in Different Groups

Muscle strength significantly (p<0.01) increased when treated with alone as well as in combination of galantamine with sodium valporate i.e. (100mg/kg SVP and 0.5mg/kg Galantamine, 100mg/kg SVP and 1mg/kg Galantamine, 200mg/kg SVP and 0.5mg/kg Galantamine, 200mg/kg SVP and 1mg/kg Galantamine) when compared to normal control group on 7th, 14th and 21st day. On 14th day there is significantly increase in muscle strength of (100mg sodium valporate +1mg Galantamine) when compared with both the doses of sodium valporate alone. Whereas on 21st day (100mg sodium valporate +1mg Galantamine) ther is significantly increased in muscle strength (Table 5) and (Figures 3-5).

**Table 5**: All values were expressed as mean ± S.E.M. (n=6), a= p<0.01 when compared with control group; b= p< 0.01 when compared to Sodium valporate, c=P<0.01 when compared to Sodium valporate(2000mg/kg) (ANOVA followed by Dunnett, s test).

| Groups | Rota road 7th day | Rota road 14th day | Rota road 21th day |
|---|---|---|---|
| Group-1 (normal) | 109 ± 3.266 | 99 ± 3.22 | 83.333 ± 2.108 |
| Group-2(100mg/kg sodium valporate) | 140.66 ± 3.661[a] | 150.83 ± 10.358[a] | 158 ± 5.066[a] |
| Group-3(200mg/kg sodium valporate) | 128.16 ± 2.93[a] | 141.5 ± 7.334[a], | 184.166 ± 6.145[a] |
| Group-4(0.5mg/kg Galantamine) | 145 ± 1.1725[a] | 157.5 ± 4.342[a], | 186.33 ± 3.373[a,b] |
| Group-5(1mg/kg Galantamine) | 135.5 ± 6.531[a] | 155.833 ± 0.9458[a], | 185 ± 1.528[a,b] |
| Group-6(100mg SVP& 0.5mgGalantamine) | 133.5± 6.313[a] | 137.166 ± 4.475[a] | 142.1666 ± 3.458[a,b,c] |
| Group-7(100mg SVP& 1mgGalantamine) | 165.16± 6.177[a,c] | 192.16 ± 1.689[a,b,c] | 206.66666 ± 4.890[a,b,c] |
| Group-8(200mg SVP& 0.5mgGalantamine) | 143± 9.790[a] | 164.3333 ± 10.426[a] | 182.83 ± 9.119[a,b] |
| Group-9(200mg SVP&1mgGalantamine) | 146.66 ± 10.706[a] | 151.333 ± 9.790[a] | 181 ± 6.303[a,b] |


How to cite this article: Nidhi Tyagi, Radha Goel, Mohd Junaid, Ravi Kumar Saini, Veerbala Singh. Effect of Galantamine with Neuropharmacological Benefits in Wistar Rats Models of Epilepsy and Behaviour. J of Pharmacol & Clin Res. 2018; 5(3): 555664. DOI: 10.19080/JPCR.2018.05.555664

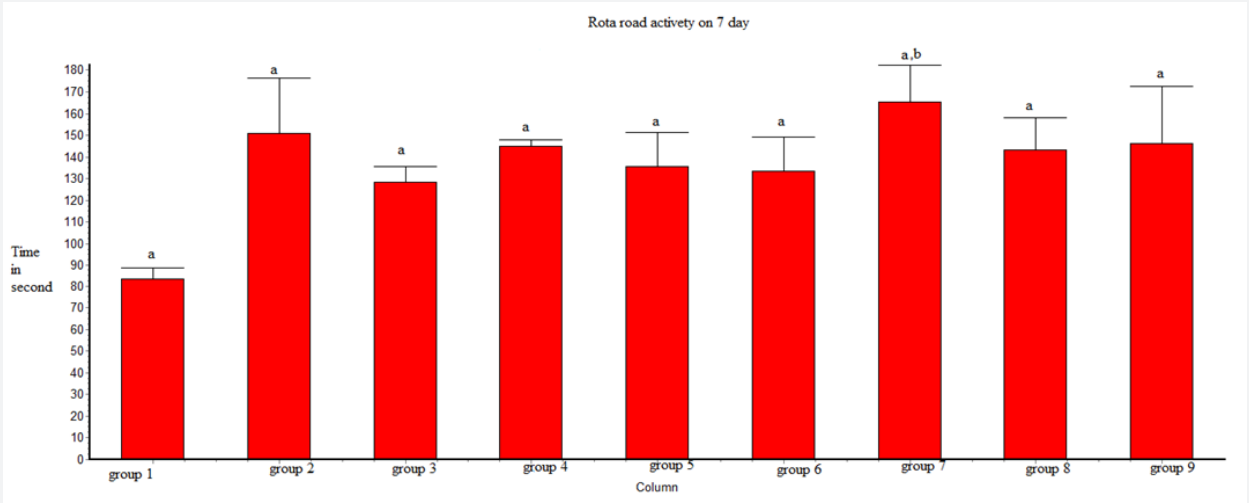


**Figure 3:** All values were expressed as mean ± S.E.M. (n=6), a= p<0.01 when compared with control group; b= p< 0.01 when compared to Sodium valporate,c=P<0.01 when compared to Sodium valporate(2000mg/kg) (ANOVA followed by Dunnett, s test).

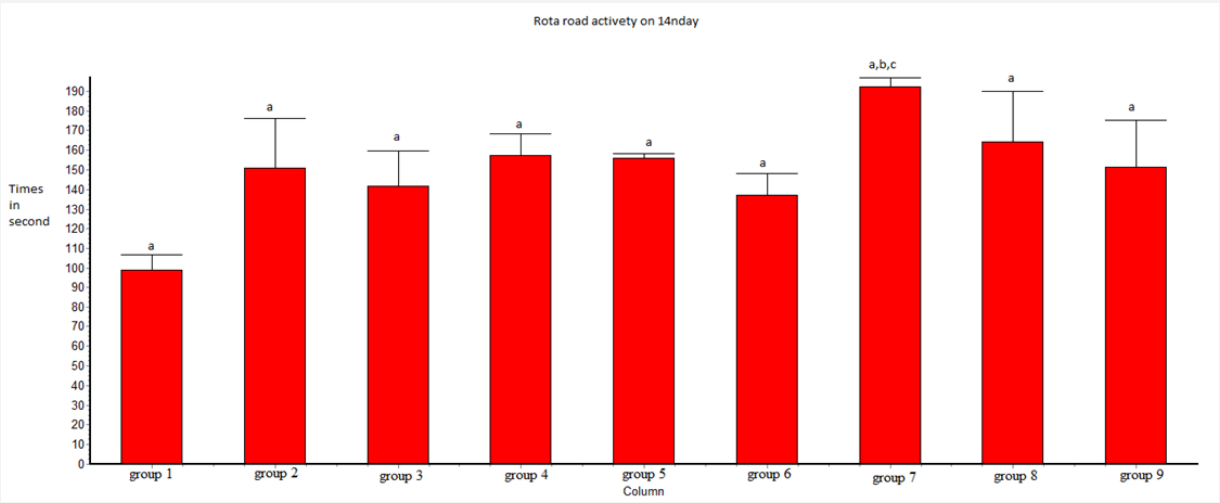


**Figure 4:** All values were expressed as mean ± S.E.M.(n=6), a= p<0.01 when compared with control group; b=p< 0.01 when compared to Sodium valporate, c=P<0.01 when compared to Sodium valporate (2000mg/kg) (ANOVA followed by Dunnett, s test).

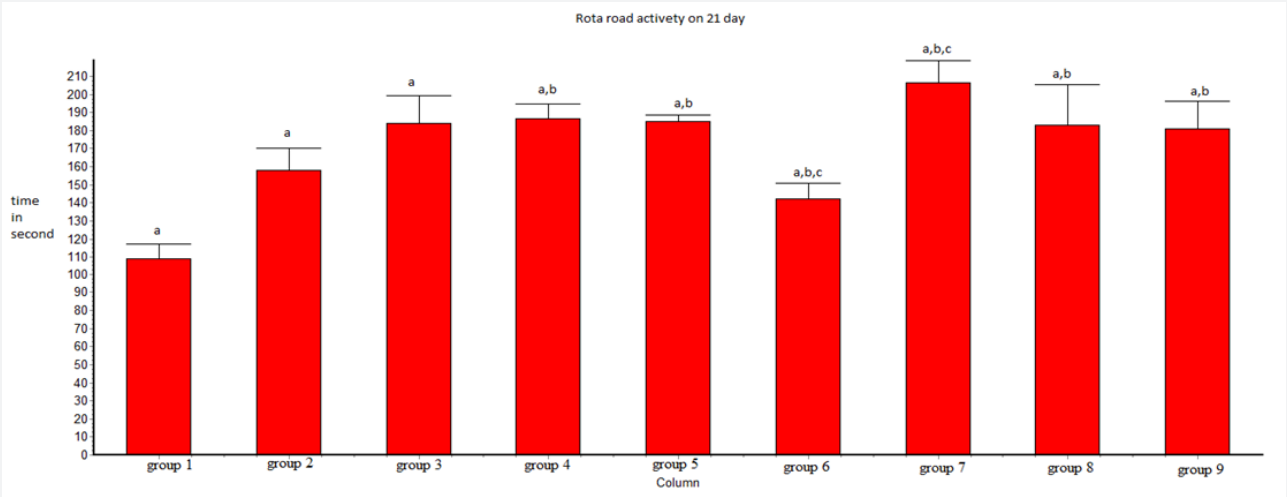


**Figure 5:** All values were expressed as mean ± S.E.M. (n=6), a= p<0.01 when compared with control group; b= p< 0.01 when compared to Sodium valporate, c=P<0.01 when compared to Sodium valporate(2000mg/kg )(ANOVA followed by Dunnett, s test).


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## Behavioural Parameters in Different Groups

Cognitive behaviour significantly ($p<0.01$) increased by when treated with alone as well as in combination of galantamine with sodium valporate i.e. (100mg/kg SVP and 0.5mg/kg Galantamine, 100mg/kg SVP and 1mg/kg Galantamine ,200mg/kg SVP and 0.5mg/kg Galantamine ,200mg/kg SVP and 1mg/kg Galantamine) when compared to normal control group on 7th, 14th and 21st day . On 14th day there is significantly increase in cognitive behaviour of (100mg sodium valporate +1mg Galantamine) when compared with both the doses of sodium valporate alone. Whereas on 21st day (100mg sodium valporate +1mg Galantamine, 200mg/kg SVP and 1mg/kg Galantamine) there is significantly increased in cognitive behavior (Table 6) and (Figures 6 & 7).

**Table 6:** All values were expressed as mean ±S.E.M.(n=6), a= p<0.01 when compared with control group; b= p< 0.01 when compared to Sodium valporate,c=P<0.01 when compared to Sodium valporate(2000mg/kg )(ANOVA followed by Dunnett,s test).

| Groups | Plus Maze 7th day | Plus Maze 14th day | Plus Maze 21th day |
|---|---|---|---|
| Group-1 (normal) | 50 ± 11.180 | 41.6666 ± 10.541 | 33.3333 ± 5.270 |
| Group-2 (100mg/kg sodium valporate) | 125 ± 9.129[a], | 162 ± 4.147[a], | 191.6666 ± 1.384[a] |
| Group-3 (200mg/kg sodium valporate) | 150 ± 9.129[a], | 158.33333 ± 5.270[a], | 170.6666 ± 4.137[a] |
| Group-4 (0.5mg/kg Galantamine) | 120.83333 ± 7.883[a], | 162.5 ± 5.590[a] | 167.6666 ± 4.137[a], |
| Group-5 (1mg/kg Galantamine) | 112.5 ± 5.590[a], | 159.1666 ± 3.449[a] | 162.5 ± 10.704[a] |
| Group-6 (100mg SVP& 0.5mg Galantamine) | 104.16666 ± 25.345 | 174.33333 ± 2.418[a] | 187.3333 ± 9.450[a] |
| Group-7(100mg SVP& 1mg Galantamine) | 125 ± 9.129[a] | 149.666 ± 5.175[a,b] | 160.16666 ± 10.104[a,b] |
| Group-8 (200mg SVP& 0.5mg Galantamine) | 120.8333 ± 15.023[a] | 141.6666 ± 12.360[a] | 154.6666 ± 6.349[a,b] |
| Group-9 (200mg SVP&1mg Galantamine) | 133.3333 ± 17.8073[a] | 163.6666 ± 2.044[a] | 158.83333 ± 8.304[a] |

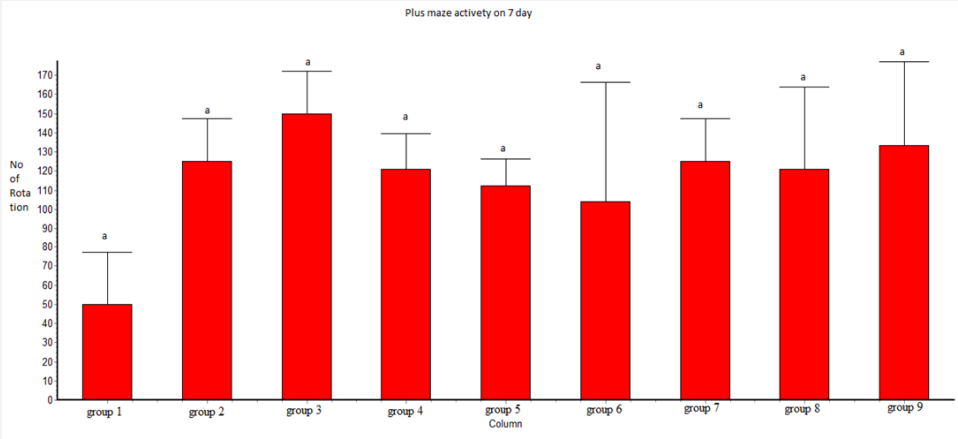


**Figure 6:** All values were expressed as mean ± S.E.M. (n=6), a= p<0.01 when compared with control group; b= p< 0.01 when compared to Sodium valporate, c=P<0.01 when compared to Sodium valporate(2000mg/kg )(ANOVA followed by Dunnett, s test).

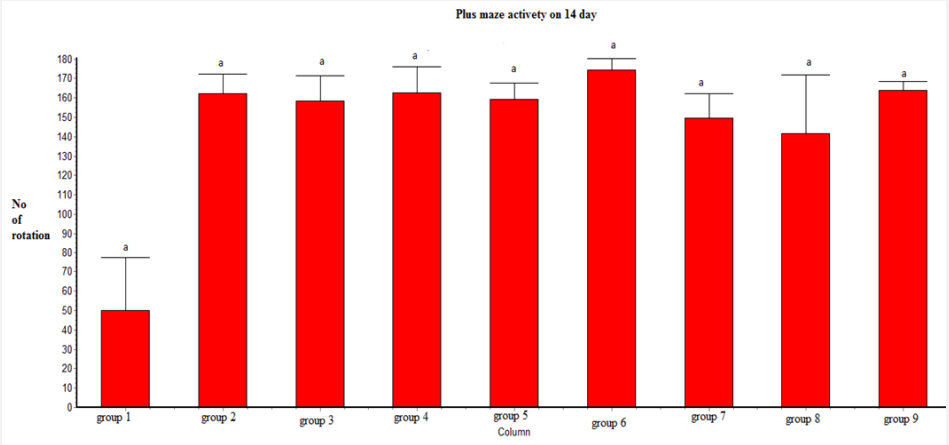


**Figure 7:** All values were expressed as mean ± S.E.M. (n=6), a= p<0.01 when compared with control group; b= p< 0.01 when compared to Sodium valporate, c=P<0.01 when compared to Sodium valporate(2000mg/kg )(ANOVA followed by Dunnett, s test).


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## Biochemical Estimation

**Biochemical Parameters in Brain Tissue:** Concentration of MDA in brain significantly (p<0.01) dicreased by when treated with alone as well as in combination of galantamine with sodium valporate i.e. (100mg/kg SVP and 0.5mg/kg Galantamine, 100mg/kg SVP and 1mg/kg Galantamine ,200mg/kg SVP and 0.5mg/kg Galantamine, 200mg/kg SVP and 1mg/kg Galantamine) when compared to normal control group and sodium valporate at both the doses (Table 7) and (Figure 8).

**Table 7:** All values were expressed as mean ±S.E.M. (n=6), a= p<0.01 when compared with control group; b= p< 0.01 when compared to Sodium valporate, c=P<0.01 when compared to Sodium valporate(2000mg/kg) (ANOVA followed by Dunnett, s test).

| Groups | Lipid Peroxides |
|---|---|
| Group 1 (normal) | 0.03192 ± 0.01861[a] |
| Group 2 (100mg/kg sodium valporate) | 0.02586 ± 0.0015[a], |
| Group 3 (200mg/kg sodium valporate) | 0.01933 ± 0.0024[a,b,c] |
| Group 4 (0.5mg/kg Galantamine) | 0.01316 ± 0.00071[a,b,c] |
| Group 5 (1mg/kg Galantamine) | 0.009292 ± 6.810[a,b,c] |
| Group 6 (100mg SVP& 0.5mgGalantamine) | 0.004612 ± 0.001720 |
| Group 7 (100mg SVP& 1mgGalantamine) | 0.0071500 ± 0.001621[a,b,c] |
| Group 8 (200mg SVP& 0.5mgGalantamine) | 0.003244 ± 0.0001141[a,b,c] |
| Group 9 (200mg SVP& 1mgGalantamine) | 0.002452 ± 0.0001272[a,b,c] |

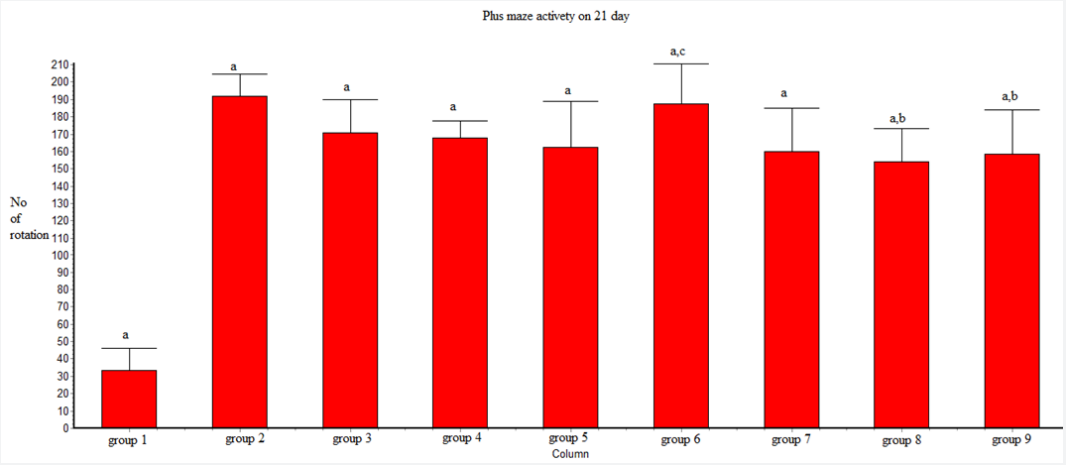


**Figure 8:** All values were expressed as mean ± S.E.M. (n=6), a= p<0.01 when compared with control group; b= p< 0.01 when compared to Sodium valporate,c=P<0.01 when compared to Sodium valporate(2000mg/kg )(ANOVA followed by Dunnett, s test).

## Biochemical Parameters in Brain Tissue

**Effect of Drug Treatment on GSH:** Concentration of GSH in brain tissue significantly (p<0.01) increased by when treated with alone as well as in combination of galantamine with sodium valporate i.e. (100mg/kg SVP and 0.5mg/kg Galantamine, 100mg/kg SVP and 1mg/kg Galantamine ,200mg/kg SVP and 0.5mg/kg Galantamine ,200mg/kg SVP and 1mg/kg Galantamine) when compared to normal control group and sodium valporate at both the doses (Table 8) and (Figure 9).

**Table 8:** All values were expressed as mean ± S.E.M. (n=6), a= p<0.01 when compared with control group; b= p< 0.01 when compared to Sodium valporate, c=P<0.01 when compared to Sodium valporate(2000mg/kg )(ANOVA followed by Dunnett, s test).

| Groups | GSH |
|---|---|
| Group 1 (normal) | 0.001302484 ± 8.422423 |
| Group 2 (100mg/kg sodium valporate) | 0.0008298174 ± 8.562477[a] |
| Group 3 (200mg/kg sodium valporate) | 0.01368 ± 1.468[a], |
| Group 4 (0.5mg/kg Galantamine) | 0.01568 ± 0.0001037[a,b,c] |
| Group 5 (1mg/kg Galantamine) | 0.06557 ± 0.0001094[a,b,c] |
| Group 6 (100mg SVP& 0.5mg Galantamine) | 0.0757 ± 0.001722[a,b,c] |
| Group 7 (100mg SVP& 1mg Galantamine) | 0.08372 ± 0.001716[a,b,c] |
| Group 8 (200mg SVP& 0.5mg Galantamine) | 0.09257 ± 0.0006074[a,b,c] |
| Group 9 (200mg SVP& 1mg Galantamine) | 0.09770 ± 0.0001242[a,b,c] |


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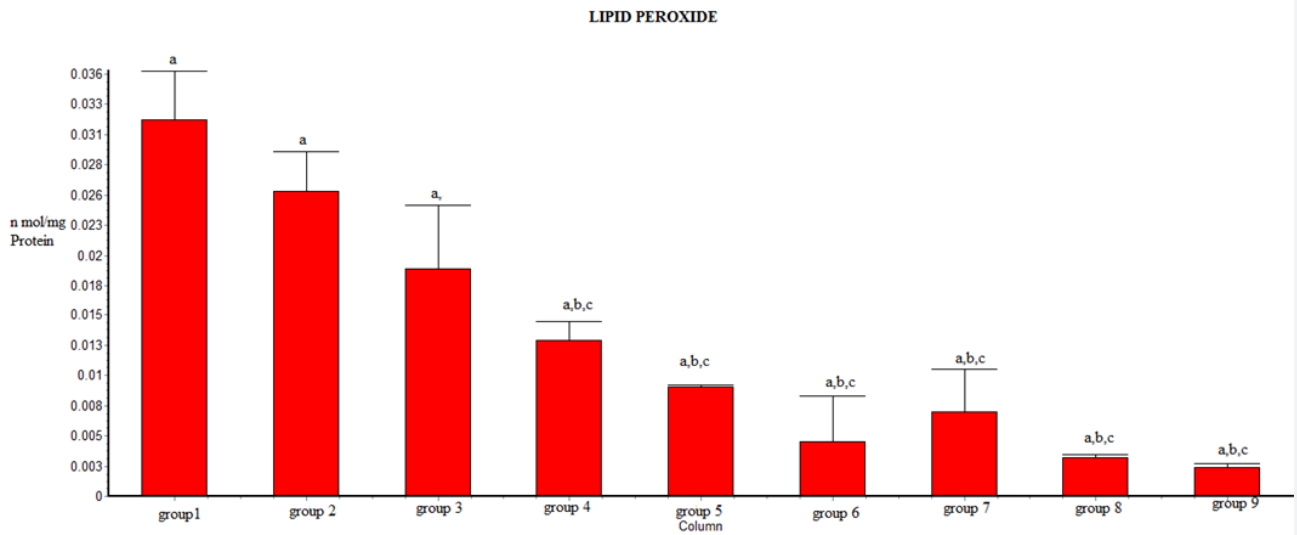


**Figure 9:** All values were expressed as mean ± S.E.M. (n=6), a= p<0.01 when compared with control group; b= p< 0.01 when compared to Sodium valporate, c=P<0.01 when compared to Sodium valporate (2000mg/kg )(ANOVA followed by Dunnett, s test).

## Effect of Sodium Valporate and Galantamine on Histopathological Evaluation of Neuropathy

This results depict that the normal functionally of hippocampus was maintained in normal control rats electric shock resulted neuron degeneration, whereas rats treated with Galantamine shows milder neuronal degeneration. Pharmacological treatment with Galantamine (0.5m/kg and 1mg/kg), sodium valporate (100mg/kg and 200mg/kg) and prevented the electric shock induce model pathological changes in brain (hippocampus) of rats. Moreover treatment with combination of sodium valporate and Galantamine. (SVP 100mg/kg + Galantamine 0.5mg/kg, SVP 100mg/kg + Galantamine 1mg/kg, SVP. 200mg/kg + Galantamine 0.5mg/kg, SVP 200mg/kg + Galantamine 1mg/kg) markedly protected changes in brain tissue (Figure 10).

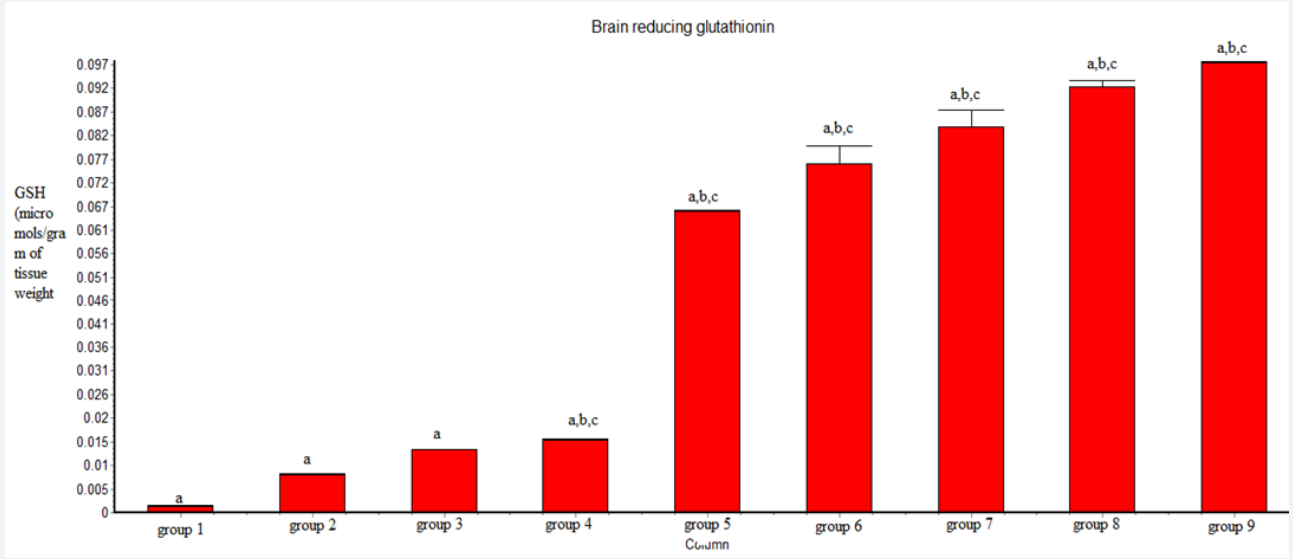


**Figure 10:** All values were expressed as mean ± S.E.M. (n=6), a= p<0.01 when compared with control group; b= p< 0.01 when compared to Sodium valporate, c=P<0.01 when compared to Sodium valporate (2000mg/kg )(ANOVA followed by Dunnett, s test).

Treated with combination of (Figure 11) SVP 100mg/kg + Galantamine 0.5mg/kg, (Figure 12) SVP 100mg/kg + Galantamine 1mg/kg, both showed decreasing neurons degeneration in brain (hippocampus). Treatment of combination (Figure 13) 200mg/kg sodium valporate + Galantamine 0.5mg/kg, (Figure 14) SVP 200mg/kg + Galantamine 1mg/kg, both showed no neurons degeneration in brain (Hippocampus). But combination of 200mg sodium valporate + 0.5mg Galantamine showed better result (Figure 15).


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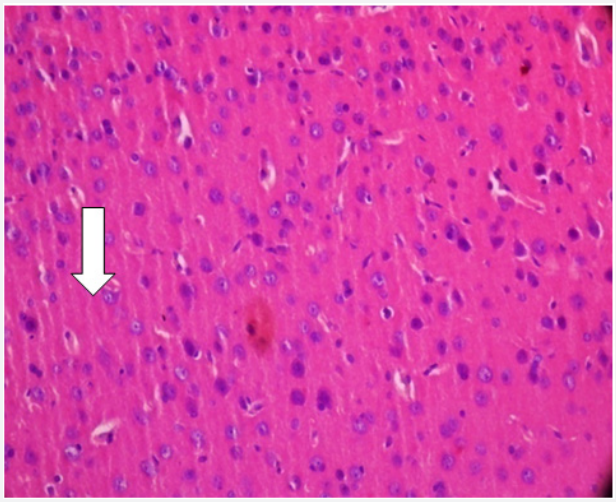

**Figure 11:** normal control group (showed neuronal degeneration in brain tissue).

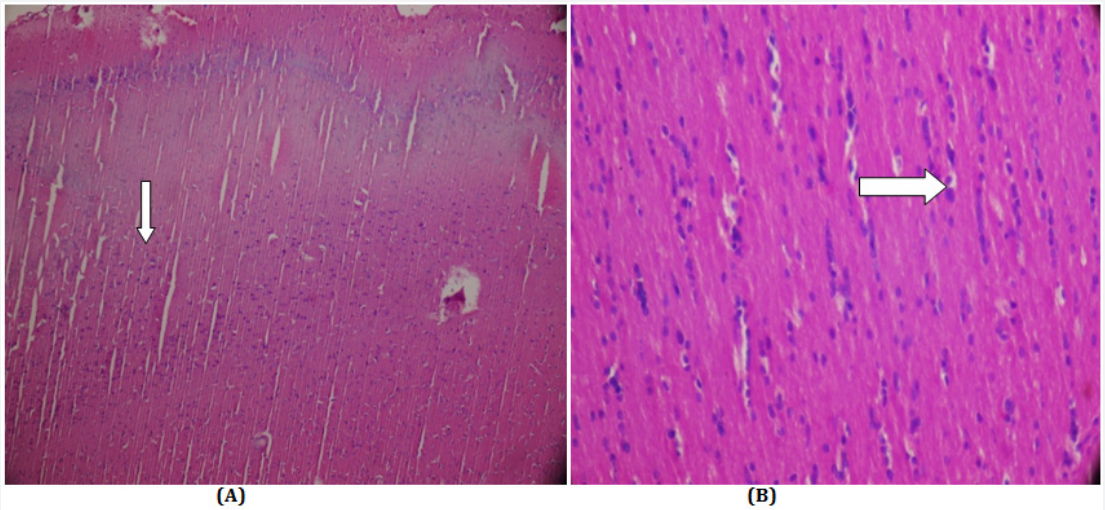


**Figure 12:** (a) Sodium valporate 100mg/kg & (b) both sodium valporate 200mg/kg showed decreasing neurons degeneration in brain tissue but sodium valporate 200mg produce better effect.

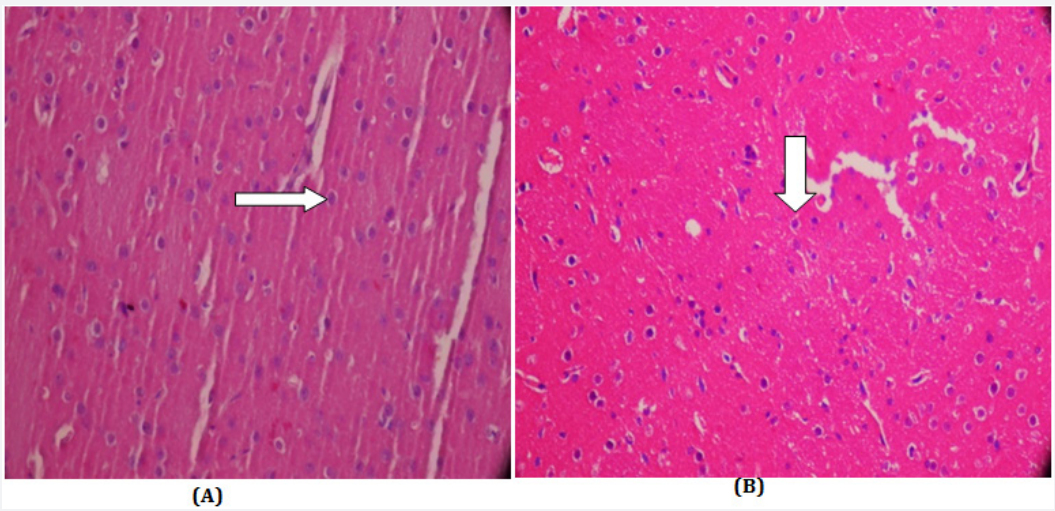


**Figure 13:** (a) Galantamine 0.5mg/kg & (b) Galantamine both 1mg/kg both showed decreasing neuronal degeneration in brain tissue. But Galantamine 1mg showed better result in comprasion to 0.5 mg Galantamine.


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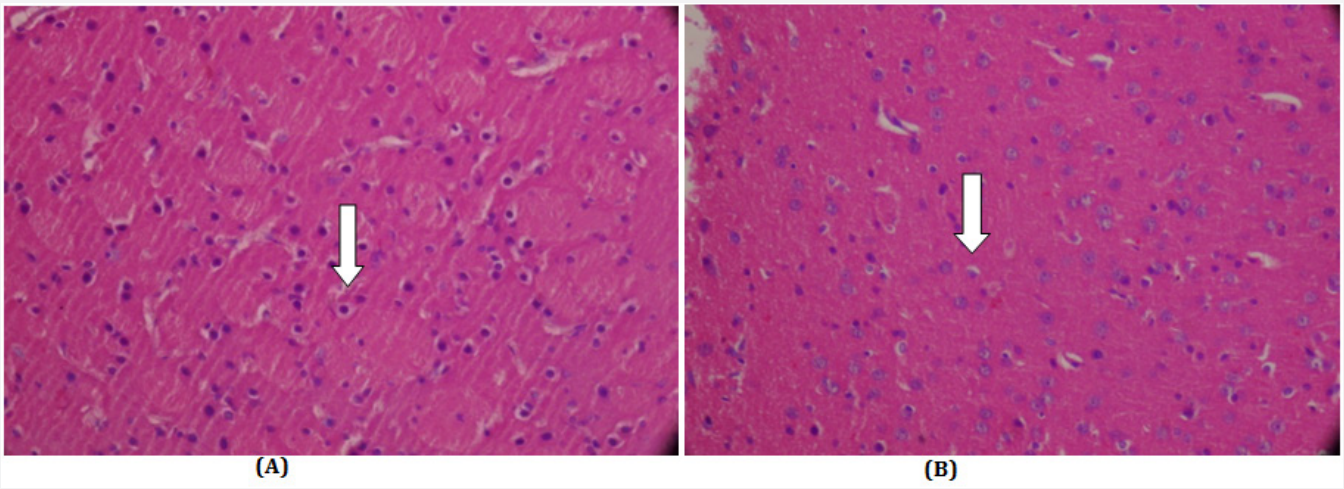


**Figure 14:** Treated with combination of (a) SVP 100mg/kg + Galantamine 0.5mg/kg, (b) SVP 100mg/kg + Galantamine 1mg/kg, both showed decreasing neurons degeneration in brain (hippocampus)

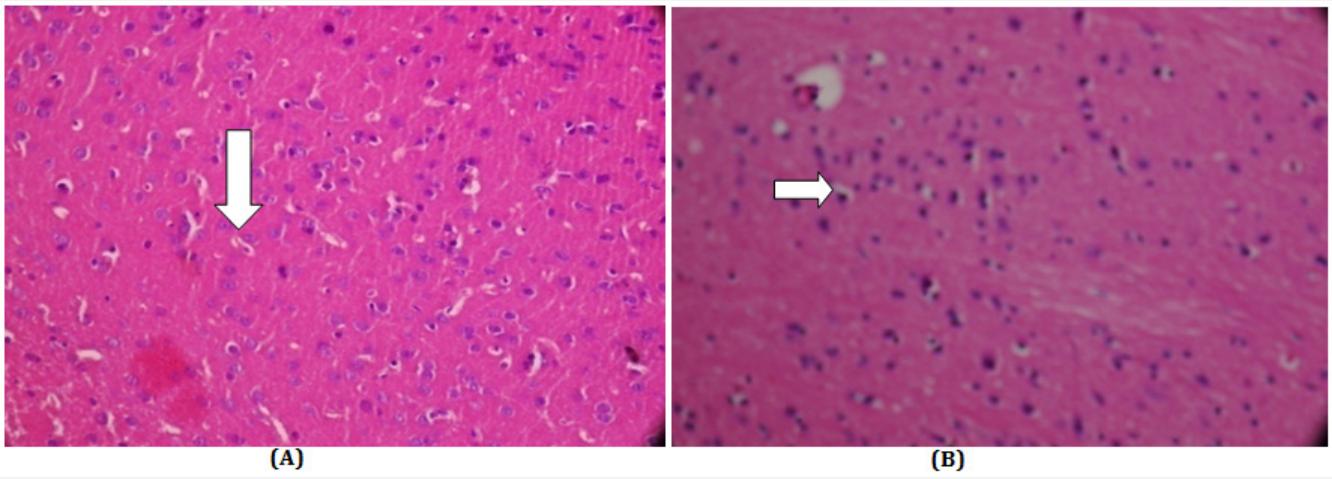


**Figure 15:** Treatment of combination (a) 200mg/kg sodium valporate + Galantamine 0.5mg/kg, (b) SVP 200mg/kg + Galantamine 1mg/kg, both showed no neurons degeneration in brain (Hippocampus). But combination of 200mg sodium valporate + 0.5mg Galantamine showed better result.

## Discussion

Epilepsy is a chronic neurological condition characterized by recurrent seizures. A seizure happens when abnormal electrical activity in the brain causes an involuntary change in body movement or function, sensation, awareness, or behavior [34]. Normally used antiepileptic drug for decreasing epileptic activity such as sodium valporate. Most of the stimuli required to induce epilepsy may cause irreversible damage of neurons. Furthermore, it is very difficult to recruit large no of humans for such type of testing. Therefore, this study conducted to evaluate and validate the effect of Galantamine in epilepsy and to wide knowledge of mechanism involved in epilepsy. In this study electric shock induce model was used to induce epilepsy in wistar rats. It is most widely employed animal model of epilepsy. The behavioral signs of sudden jurk in the body and body is hyper active have been reported. The behavioral alteration like spontaneous behavior alteration, and rotaroad activity was used for noted to occur within one week subsequent to the surgery [35,36].

The electric shock model is relevant for understanding epilepsy, as in epilepsy neuronal damage is main cause of brain disorder in humans. Galantamine can abile to decrease the oxidative stress and decrease the cholinesterase concentration caused due to epilepsy. And it is also treat cognitive impairment [37]. Treatment with Galantamine (0.5mg/kg) and (1mg/kg) and combination with sodium valporate (100mg/kg SVP and 0.5mg/kg Galantamine, 100mg/kg SVP and 1mg/kg Galantamine ,200mg/kg SVP and 0.5mg/kg Galantamine ,200mg/kg SVP and 1mg/kg Galantamine) showed significantly effect on behavioral (when compared to normal control group on 7$^{th}$, 14$^{th}$ and 21$^{st}$ day . On 14$^{th}$ day there is significantly increase in muscle strength of (100mg sodium valporate +1mg Galantamine) when compared


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with both the doses of sodium valporate alone. Whereas on 21st day (100mg sodium valporate +1mg Galantamine) there is significantly increased in muscle strength on rotaroad activity, when compared to normal control group on 7th, 14th and 21st day . On 14th day there is significantly increase in cognitive behavior of (100mg sodium valporate +1mg Galantamine) when compared with both the doses of sodium valporate alone.

Whereas on 21st day (100mg sodium valporate +1mg Galantamine, 200mg/kg SVP and 1mg/kg Galantamine) there is significantly increased in cognitive behavior in plus maze activity). as well as biochemical estimation parameter (Concentration of MDA in brain significantly ($p<0.01$) decreased by when treated with alone as well as in combination of Galantamine with sodium valporate i.e. (100mg/kg SVP and 0.5mg/kg Galantamine, 100mg/kg SVP and 1mg/kg Galantamine, 200mg/kg SVP and 0.5mg/kg Galantamine, 200mg/kg SVP and 1mg/kg Galantamine) when compared to normal control group and sodium valporate at both the doses in lipid peroxide method. Concentration of GSH in brain tissue significantly ($p<0.01$) increased by when treated with alone as well as in combination of Galantamine with sodium valporate i.e. (100mg/kg SVP and 0.5mg/kg Galantamine, 100mg/kg SVP and 1mg/kg Galantamine, 200mg/kg SVP and 0.5mg/kg Galantamine, 200mg/kg SVP and 1mg/kg Galantamine) when compared to normal control group and sodium valporate at both the doses in GSH method).

In histopathological study of hippocampus showed neuronal degeneration normal control group (showed neuronal degeneration in tissue in brain tissue), Sodium valporate 100mg/kg and both sodium valporate 200mg/kg showed decreasing neurons degeneration in brain tissue but sodium valporate 200mg produce better effect, Galantamine 0.5mg/kg and Galantamine both 1mg/kg both showed decreasing neuronal degeneration in brain tissue. But Galantamine 1mg showed better result in compression to 0.5 mg Galantamine. Treated with combination of SVP 100mg/kg + Galantamine 0.5mg/kg, SVP 100mg/kg + Galantamine 1mg/kg, both showed decreasing neurons degeneration in brain (hippocampus). Treatment of combination 200mg/kg sodium valporate + Galantamine 0.5mg/kg, SVP 200mg/kg + Galantamine 1mg/kg, both showed no neurons degeneration in brain (Hippocampus). But combination of 200mg sodium valporate + 0.5mg Galantamine showed better result. All groups sowed significant role in comparison to control group.

## Conclusion

Epilepsy is a disorder of the central nervous system characterized by periodic loss of consciousness with or without convulsions associated with abnormal electrical activity in the brain. There are 50 million people living with epilepsy worldwide, and most of them reside in developing countries. About 10 million persons with epilepsy are there in India. Though there are multiple pharmacological treatment option for epilepsy but it is complicated to treat primarily because of involvement of numerous mediators in its Pathophysiology and its resistance to medications. The drugs employed clinically in treatment and management of epilepsy are associated with multiple other adverse effects which additionally make its treatment more difficult thus this research was aimed at examining Galantamine in epilepsy and open new vistas in treatment and management of this disease. Galantamine was found to have positive effect in epilepsy induced by Increasing Current Electroshock Seizures test of wistar rats. The drug can therefore offer an alternative approach in epilepsy state.

Conclusively, additional investigation is required on other animal models to obtain a dependable oversight of the outcome of Galantamine on epilepsy in actual clinical scenario. Treatment with Galantamine (0.5mg/kg) and (1mg/kg) and combination with sodium valporate (100mg/kg SVP and 0.5mg/kg Galantamine, 100mg/kg SVP and 1mg/kg Galantamine ,200mg/kg SVP and 0.5mg/kg Galantamine ,200mg/kg SVP and 1mg/kg Galantamine) showed significantly effect on behavioral (when compared to normal control group on 7th, 14th and 21st day . On 14th day there is significantly increase in muscle strength of (100mg sodium valporate +1mg Galantamine) when compared with both the doses of sodium valporate alone. Whereas on 21st day (100mg sodium valporate +1mg Galantamine) there is significantly increased in muscle strength on rotaroad activity, when compared to normal control group on 7th, 14th and 21st day. On 14th day there is significantly increase in cognitive behavior of (100mg sodium valporate +1mg Galantamine) when compared with both the doses of sodium valporate alone. Whereas on 21st day (100mg sodium valporate +1mg Galantamine, 200mg/kg SVP and 1mg/kg Galantamine) there is significantly increased in cognitive behavior in plus maze activity).

As well as biochemical estimation parameter (Concentration of MDA in brain significantly ($p<0.01$) decreased by when treated with alone as well as in combination of Galantamine with sodium valporate i.e. (100mg/kg SVP and 0.5mg/kg Galantamine, 100mg/kg SVP and 1mg/kg Galantamine ,200mg/kg SVP and 0.5mg/kg Galantamine ,200mg/kg SVP and 1mg/kg Galantamine) when compared to normal control group and sodium valporate at both the doses in lipid peroxide method. Concentration of GSH in brain tissue significantly ($p<0.01$) increased by when treated with alone as well as in combination of Galantamine with sodium valporate i.e. (100mg/kg SVP and 0.5mg/kg Galantamine, 100mg/kg SVP and 1mg/kg Galantamine, 200mg/kg SVP and 0.5mg/kg Galantamine, 200mg/kg SVP and 1mg/kg Galantamine) when compared to normal control group and sodium valporate at both the doses in GSH method). In histopathological study of hippocampus showed neuronal degeneration normal control group (showed neuronal degeneration in tissue in brain tissue), Sodium valporate 100mg/kg and both sodium valporate 200mg/kg showed decreasing neurons degeneration in brain tissue but sodium valporate 200mg produce better effect, Galantamine 0.5mg/kg


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and Galantamine both 1mg/kg both showed decreasing neuronal degeneration in brain tissue.

But Galantamine 1mg showed better result in compression to 0.5 mg Galantamine. Treated with combination of SVP 100mg/kg + Galantamine 0.5mg/kg, SVP 100mg/kg + Galantamine 1mg/kg, both showed decreasing neurons degeneration in brain (hippocampus). Treatment of combination 200mg/kg sodium valporate + Galantamine 0.5mg/kg, SVP 200mg/kg + Galantamine 1mg/kg, both showed no neurons degeneration in brain (Hippocampus). But combination of 200mg sodium valporate + 0.5mg Galantamine showed better result. All groups sowed significant ($p<0.01$) role in comparison to control group.

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