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Original Research Article

A comparative study of effect of phenytoin, topiramate, and zonisamide in learning and memory of albino rats

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ABSTRACT

Background: Epilepsy is one of the non-communicable neurologic diseases leading to significant morbidity and mortality. Complaints of impaired learning and memory are common in patients of epilepsy. Antiepileptic drugs (AEDs) may further enhance this impairment. So, the present study was carried out on albino rats to evaluate the effect of AEDs on learning and memory.
Methods: Albino rats of about 150 -200 gm of either sex were treated with drugs for 15 days and assessed for effect on learning behavior and again treated for next 15 days after which they were assessed for retention behavior on Morris water maze and Elevated plus maze. The data was statistically analyzed by ANOVA and Tukey HSD.
Results: Phenytoin and topiramate causes significant delay in learning and memory whereas zonisamide doesn't causes significant delay in learning and memory.
Conclusions: Impairment in learning and memory occurs in treatment with phenytoin and topiramate but not with zonisamide in low therapeutic doses.

Keywords: Learning and memory, Phenytoin, Topiramate, Zonisamide

INTRODUCTION

Learning is an act or process of acquiring knowledge or skill by means of study, practice or some experience and subsequent retention of that information is called memory.

Learning and memory are most important part of cognition. Effects of a wide variety of pharmacological agents or brain lesions on cognitive behavior has been studied and most validly interpreted as "enhancement or impairment" of learning processes.

Epilepsy is among a condition in which there is impairment of learning and memory process. The learning and memory impairment can have multiple causes in epilepsy, the most important being brain lesions, seizures, epileptic dysfunction, and treatment by anti-epileptic drugs.

Epilepsy is one of the most prevalent non-communicable neurologic diseases leading to significant disability and mortality.[1]

Epilepsy is a chronic condition of recurrent seizures that can also vary from brief and nearly undetectable symptoms to periods of vigorous shaking and convulsions.[2] Complaints of impaired learning and memory are common in patients of epilepsy. Anti-epileptic drugs (AEDs) may further enhance this impairment. So, study of effect of AEDs on learning and memory is of particular importance.

Learning and memory are most important part of cognition. So, impairment of learning and memory function can also be stated in terms of impaired cognition. All commonly used AEDs have some effect on cognitive function. The effect become substantial when crucial functions are involved. For example, learning in children, driving ability in adults or when already vulnerable functions are involved, such as memory in elderly patients.

It is important to understand that whether the impairment is caused by the disease itself or by the AEDs so that further preventive measures will be taken. But it is difficult to distinguish between impairment associated with the disorder and those attributable to the drugs used for treatment. In an attempt to isolate the cognitive deficits associated with the drugs themselves, this study investigates the effects of antiepileptic compounds on learning and memory in normal animal.

The new AEDs might produce less impairment of cognitive functions but this aspect has not been systematically studied.[3] But several reports have suggested that newer AEDs such as topiramate and zonisamide may have fewer effects on cognition as compared older drugs. This study compares cognitive impairment caused by one of the more commonly used first generation anti-epileptic drug, phenytoin with that of two second genaration antiepileptic drug topiramate and zonisamide.[4,5]

Phenytoin is one of the most widely prescribed antiepileptic compound. Since the discovery of the powerful anticonvulsant properties of phenytoin, it has been used extensively in the treatment of tonic-clonic and partial seizures.[6-8] Recent evidence suggests that despite the success in controlling these types of seizures, phenytoin has negative effects on learning and memory processes.[9] Topiramate (TPM), as an antiepileptic drug (AED). It reduces voltage-gated Na^+ currents in cerebellar granule cells and may act in a manner similar to phenytoin. It highly effective in the treatment of seizure disorders and migraine headaches, and has promise for use in psychiatric disorders and obesity.[10-12]

Zonisamide is a broad spectrum antiepileptic drug with multiple mechanisms of action which has been recently approved. Zonisamide inhibits both the T-type Ca2+ currents and the sustained, repetitive firing of spinal cord neurons, presumably by prolonging the inactivated state of voltage-gated Na+ channels in a manner similar to that of phenytoin. The effects of zonisamide on cognition have not been studied as extensively as have those of first generation drugs. Some study shows that it may have fewer cognitive side effect.[13] Rats are chosen for this study as they are particularly suitable for testing psychopharmacological agents because they can be trained properly for various types of work performances including development of conditioned reflexes.[14] Therefore, this study is undertaken to made an effort for the assessment of the effect of phenytoin, topiramate and zonisamide on learning and memory in albino rats.

METHODS

This study has been done in the Department of Pharmacology and Therapeutics, Rajendra Institute of Medical Sciences, Ranchi.

Male Wister albino rats are used for this study. They are most standardized of all experimental animals. They are particularly suitable for testing of psychopharmacological study because they can be trained properly for various types of performances including development of conditioned reflex. Gender has been shown to affect both antiepileptic efficacy and elimination kinetics of antiepileptic drugs in rats. Taking this into account, in the present study, only male Wistar rats were used so that any differences in the results could be attributed to the study compound.[15]

The animals were kept in standard laboratory conditions with a natural light and dark cycle. They were acclimatized to the available housing condition for one week and were fed with standard laboratory diet and water was given ad libitum. Animals were randomly selected in four groups of six animals each.

Group A was control group, group B was given Phenytoin, Group C was given Topiramate and Group D was given Zonisamide.

- Gum acacia:1% Gum acacia suspension was prepared by mixing 1 gm of Gum acacia and small amount of water in a mortar pestle and then making a final suspension in 100 ml distilled water.
- Phenytoin: Daily dose 300mg of human anti-epileptic dose was chosen. Using conversion factor of 0.018 a daily dose of 27mg/kg was calculated.[16-18]
- Topiramate: human anti-epileptic dose of 200mg per day was chosen.[19] Using conversion factor of 0.018 daily dose of 18mg/kg was calculated.
- Zonisamide: Daily dose of 200mg of human anti-epileptic dose was selected.[20] Using conversion factor of 0.018 daily dose of 18mg/kg was calculated.

All the rats had received respective treatment for the period of 15 days. On Day 0 reading rats were tested one day prior to treatment on both morris water maze ans elevated plus maze. Then rats had received the treatment for 15 days. Then they were examined for their learning behavior on Morris water maze and elevated plus maze, for five continuous days (day16 to day 20) after 15 days of treatment. The rats then again received all the respective treatment for next 15 days after which they were examined again (on day 35) on Morris water maze and elevated plus maze to evaluate retention of past event (memory). Apparatus Morris water maze (MWM) The Morris water maze is one of the most widely used tasks in behavioral neuroscience for studying the psychological

processes and neural mechanisms of spatial learning and memory.[21] It Consist of a large circular tank of diameter 1.8-2.0 m and 0.4-0.5m in height. The pool is filled with water and rendered opaque by addition of non-toxic color. The tank is marked off into four quadrants, i.e. North, South, East and West. An escape platform of 13 cm square size with heavy base is placed in middle of any fixed quadrant. To hide the platform water is added to a level 2 cm above the platform. The room should have potential extra maze cues that help to navigate the tank. Procedure Rats were placed in the water at a designated starting location and the time to find the hidden platform from the starting point is defined as "Escape Latency". Each rat was tested for two trials/day with inter trial period of two minute during which they were placed in their home cage.[22] Elevated Plus Maze (EPM) It is a validated method to test parameters of learning and memory to evaluate spatial long term memory in rodents. Introduced by Pellow (1985) in rats based on apparent natural aversion of rodents to open and high spaces. Based on this Etoh et al. has demonstrated that transfer latency was markedly shortened if the animal had previously experienced entering in closed arm, and this shortening has been related to memory process. Apparatus for rat consist of two open (50 x 10 cm) and two enclosed arms (50x10x40 cm). The entire maze is elevated to a height of 50 cm.

Procedure The rats were placed at the edge of open arm with facing away from the closed arm. Transfer latency is the elapsed time between the time the animal is placed in the open arm and the time in which all its leg has crossed a line marking initiation of closed arms.[23]

Each rat was examined twice/day on successive open arm and time to reach in closed arm was noted by stopwatch.

Statistical analysis of data was carried out by employing analysis of variance (Snedecor and Cochran, 1967). One way ANOVA test was used to compare the effect of drugs on different group the effect. Tukey's HSD test was used for post-hoc analysis of significant overall differences control.[24]

RESULTS

Table 1 is showing the averages of time taken to reach the platform in seconds (Escape latency time) of two trials/day for control group on Morris water maze. Table 2 shows averages of time (in sec) taken to reach closed arms (Transfer latency time) of two trials/day for control group on Elevated plus maze.

From Table 1 and Table 2, we can see that there is decrease in escape and transfer latency for control group in both morris water maze and elevated plus maze.

Table 1: Mean and standard deviation of group A on morris water maze for escape latency.

Group A on morris water maze for escape latency							
Mean	60.79	52.66	42.66	32.75	22.08	14.79	10.00
SD	11.27	8.51	4.34	3.51	4.86	5.43	4.04

SD: Standard deviation

Table 2: Mean and standard deviation of group A on elevated plus maze for transfer latency.

Group A on elevated plus maze for transfer latency							
Mean	49.41	42.50	34.58	28.33	20.41	12.91	8.91
SD	9.23	8.56	6.48	4.86	4.28	2.67	1.15

SD: Standard deviation

Performance of phenytoin group

The Table 3 shows Escape latency time of two trials/day for Phenytoin group on Morris water maze. The Table 4 shows transfer latency time of two trials/day for phenytoin group on elevated plus maze. From Table 3 and Table 4, we see that there is delayed learning in case of phenytoin in both morris water maze and elevated plus maze, when compared to control. The difference is significant on day 18, 19, 20, and on day 35 (Table 9 and Table 10).

Performance of topiramate groups

The Table 5 shows Escape latency time of two trials/day for Topiramate group on Morris water maze. The Table 6 shows Transfer latency time of two trials/day for topiramate group on elevated plus maze.

Table 3: Mean and standard deviation of group B on morris water maze for escape latency.

Group B on morris water maze for escape latency							
Mean	60.58	54.50	51.66	48.41	46.25	45.00	43.41
SD	17.08	15.18	12.65	10.53	11.12	14.50	13.16

SD: Standard deviat

Table 4: Mean and standard deviation of group A on elevated plus maze for transfer latency.

Group A on Elevated plus maze for transfer latency							
Mean	49.00	46.00	42.25	39.33	36.25	33.08	31.16
SD	9.13	8.49	7.34	5.92	6.80	6.53	6.46

SD: Standard deviation

Table 5: Mean and standard deviation of group C on morris water maze for escape latency.

Group C on morris water maze for escape latency							
Mean	60.08	52.50	48.00	44.16	40.91	39.08	37.83
SD	12.07	12.08	12.03	11.25	12.58	13.19	12.51

SD: Standard deviation

Table 6: Mean and standard deviation of group C on elevated plus maze for transfer latency.

Group C on elevated plus maze for transfer latency							
Mean	50.66	46.50	41.25	37.41	33.58	30.00	27.00
SD	13.84	12.24	12.63	9.35	11.17	11.12	10.72

SD: Standard deviation

Table 7: Mean and standard deviation of group D on morris water maze for escape latency.

Group D on morris water maze for escape latency							
Mean	60.08	52.08	45.00	38.41	32.41	27.75	24.00
SD	11.53	10.62	12.83	10.61	9.24	8.079	7.56

SD: Standard deviation

Table 8: Mean and standard deviation of group D on elevated plus maze for transfer latency.

Group D on elevated plus maze for transfer latency							
Mean	50.50	43.41	37.75	31.83	26.00	22.16	19.08
SD	6.83	6.57	5.10	5.78	5.14	3.76	4.81

SD: Standard deviation

From Table 5 and Table 6, we see that there is delayed learning in case of topiramate in both morris water maze and elevated plus maze, when compared to control.

The difference is significant on day 19, 20, and day 35 (Table 9 and Table 10).

Performance of Zonisamide group

The Table 7 shows escape latency time of two trials/day for zonisamide group on morris water maze. The Table 8 shows transfer latency time of two trials/day for zonisamide group on elevated plus maze.

From Table 7 and Table 8, we see that there is delayed learning in case of zonisamide in both morris water maze and elevated plus maze, when compared to control, but this is not significant.

In day 35 there is significant difference in results between phenytoin and zonisamide in both elevated plus maze and morris water maze (Table 9 and Table 10).

DISCUSSION

Phenytoin versus other groups in this study

Phenytoin causes significant impairment in learning and memory as compared to control group in both Morris water maze and elevated plus maze as seen in Table 3 and Table 4.

It showed significant difference in learning from day 18 in both morris water maze ($p < 0.045$) and elevated plus maze when compared with control. On day 19^{th} ($p < 0.02$) and 20^{th} ($p < 0.01$), the difference in learning was even more significant) as compared to control in both the animal models used (Table 9 and Table 10).

The difference was not significant when compared to topiramate. On day 35, the testing day for memory (retention of past event) the difference was significant as compared to control and zonisamide in morris water maze ($p < 0.016$) and elevated plus maze ($p < 0.026$). Phenytoin is a commonly and effectively used AED, effective against all types of partial and tonic-clonic

seizures but not absence seizures. Phenytoin treatment has been shown to be associated with cognitive decline with increasing the risk of cognitive side effects.[25-27]

Table 9: Comparison of all the groups for escape latency time on morris water maze.

	Group	Group	Mean difference	Significance
Day 0	A	B	0.2083	1.000
		C	0.7083	1.000
		D	0.7083	1.000
	B	C	0.5000	1.000
		D	0.5000	1.000
	C	D	0.0000	1.000
Day 16	A	B	-1.833	0.993
		C	0.1666	1.000
		D	0.5833	1.000
	B	C	2.000	0.991
		D	2.333	0.986
	C	D	0.4166	1.000
Day 17	A	B	-9.000	0.508
		C	-5.333	0.837
		D	-2.333	0.983
	B	C	3.667	0.938
		D	6.667	0.726
	C	D	3.000	0.965
Day 18	A	B	-15.666	0.045
		C	-11.416	0.195
		D	-5.583	0.734
	B	C	4.250	0.866
		D	10.000	0.294
	C	D	5.750	0.725
Day 19	A	B	-24.167	0.002
		C	-18.833	0.017
		D	-10.333	0.298
	B	C	5.333	0.787
		D	13.833	0.105
	C	D	8.500	0.463
Day 20	A	B	-30.208	0.001
		C	-24.291	0.005
		D	-12.958	0.203
	B	C	5.916	0.786
		D	17.250	0.058
	C	D	11.333	0.305
Day 35	A	B	-33.416	0.000
		C	-27.833	0.001
		D	-14.000	0.107
	B	C	5.583	0.772
		D	19.416	0.016
	C	D	13.833	0 .112

Likewise, Trimble and Thompson reported a change in mental state of cognition in healthy volunteers while being treated with phenytoin. The results in this study are consistant with these findings. Thus, these data suggest that there is an apparent learning and memory deficits associated with phenytoin. There is a need to be careful when prescribing this drug, particularly in vulnerable population like children, where long-term developmental considerations need to be accounted.

Table 10: Comparison of all groups for transfer latency on elevated plus maze.

	Group	Group	Mean difference	Significance
Day 0	A	B	0.4167	1.000
		C	-1.250	0.996
		D	-1.083	0.998
	B	C	-1.667	0.992
		D	-1.500	0.994
	C	D	0.166	1.000
Day 16	A	B	-3.500	0.911
		C	-4.000	0.874
		D	0.9167	0.998
	B	C	-0.500	1.000
		D	2.583	0.961
	C	D	3.083	0.937
Day 17	A	B	-7.667	0.410
		C	-6.667	0.528
		D	-3.167	0.913
	B	C	-1.000	0.997
		D	4.500	0.790
	C	D	3.500	0.887
Day 18	A	B	-11.000	0.046
		C	-9.083	0.121
		D	-3.500	0.803
	B	C	1.916	0.959
		D	7.500	0.244
	C	D	5.583	0.489
Day 19	A	B	-15.833	0.007
		C	-13.167	0.026
		D	-5.5833	0.564
	B	C	2.667	0.922
		D	10.250	0.106
	C	D	7.583	0.308
Day 20	A	B	-20.167	0.000
		C	-17.083	0.002
		D	-9.250	0.123
	B	C	3.083	0.863
		D	10.916	0.054
	C	D	7.833	0.228
Day 35	A	B	-22.250	0.000
		C	-18.083	0.001
		D	-10.166	0.072
	B	C	4.1667	0.710
		D	12.080	0.026
	C	D	-7.916	0.208

Topiramate versus other groups in this study

Topiramate causes significant impairment in learning and memory as compared to control group in both Morris water maze and elevated plus maze as seen in Table 5 and Table 6 on day 19. On comparing with phenytoin, the

results were similar. On day 20 the difference in learning was more significant on day 20 with control group. The difference was not significant with phenytion and zonisamide.

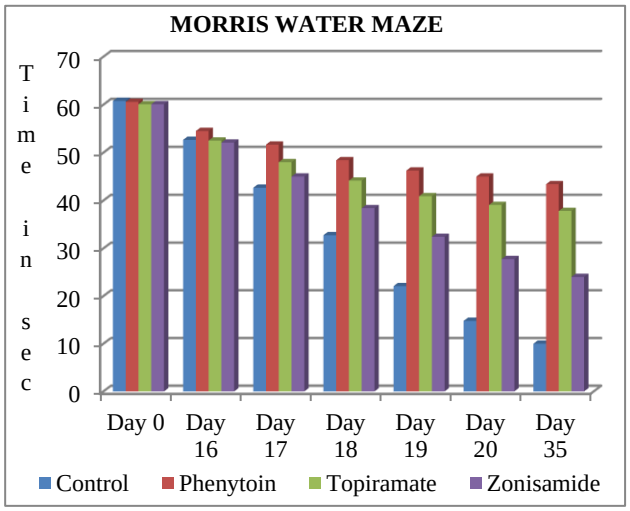

Figure 1: Comparison of all four groups for their performances on morris water maze.

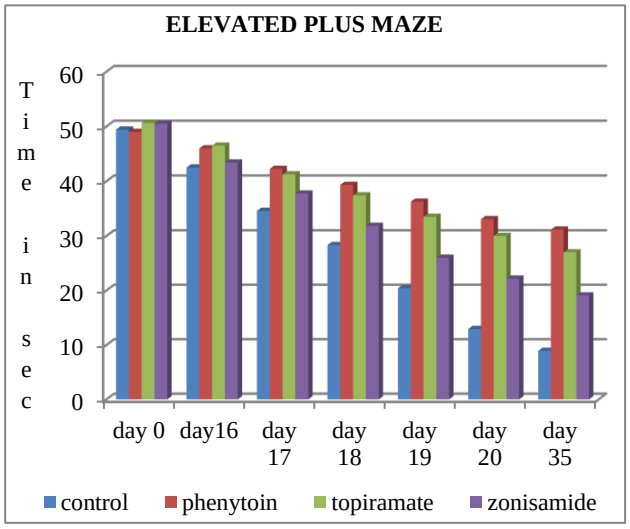

Figure 2: Comparison of all four groups for their performances on elevated pus maze.

On day 35, testing day for memory (retention of past event) the difference was significant (Table 9 and Table 10) when compared to control in both morris water maze ($p < 0.001$) and elevated plus maze ($p < 0.001$). The difference was not significant when compared to phenytoin and zonisamide either of the animal models.

Topiramate is a sulfamate substituted monosaccharide that has multiple actions and is effective as adjunctive therapy for partial and primary generalized tonic clonic seizures. Some previously documented studies support our results where topiramate administration in epileptic patients has impaired memory.[28-30] The results in this study showed similar results to those studies.

Zonisamide versus other groups in this study

In this study, from Table 7 and Table 8, it is seen that there is significant difference on day 35, when compared with phenytoin on both morris water maze, $p < 0.016$ (Table 9) and elevated plus maze, $p < 0.026$, (Table 10). The difference was not significant when compared to control and topiramate group during the whole study period. It is seen that zonisamide showed least decline in learning and memory process of albino rats in morris water maze and elevated plus maze when compared to phenytoin and topiramate.

The difference in learning and memory was not significant (Table 9 and Table 10) when compared to control and topiramate. On day 35 zonisamide group showed significant difference in memory on comparison to phenytoin on morris water maze ($p < 0.016$) and elevated plus maze ($p < 0.026$). Its effect on learning and memory by some studies have concluded that there is no cognitive side effect of zonisamide in low doses (200mg daily).[31,32] Our study results was similar to their study, while some study says that it has poor effect on long term use in cognition.[33,34] Results in this study conflicts from those studies. In this study, we have used zonisamide in low therapeutic doses. So, it can be said that in lower limit of normal therapeutic doses it has lesser cognitive side effect as compared to phenytoin.

From our observations, we can say that all the three antiepileptic drugs in our study i.e. phenytoin, topiramate and zonisamide are causing delay in learning and memory as compared to the control group in both Morris water maze and Elevated plus maze (Figure 1 and Figure 2). On comparison among groups the delay in learning and memory in significant for phenytoin and topiramate when compared with control. The difference in learning and memory was significant between phenytoin and zonisamide on day 35.

CONCLUSION

It is seen that decline in learning and memory is a known side effect of most of the antiepileptic drugs. This is also seen in this study.

But, this was not significant for zonisamide at lower therapeutic doses, hence zonisamide doesn't cause impairment of learning and memory when used in lower therapeutic doses. Further studies needed to analyse the effect of these drugs in learning and memory in long term uses.

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