TO CARRY OUT PHARMACOLOGICAL EVALUTION OF BISACURONE ON PENTYLENETETRAZOLE (PTZ) - INDUCED CONVULSIONS IN LABORATORY MICE

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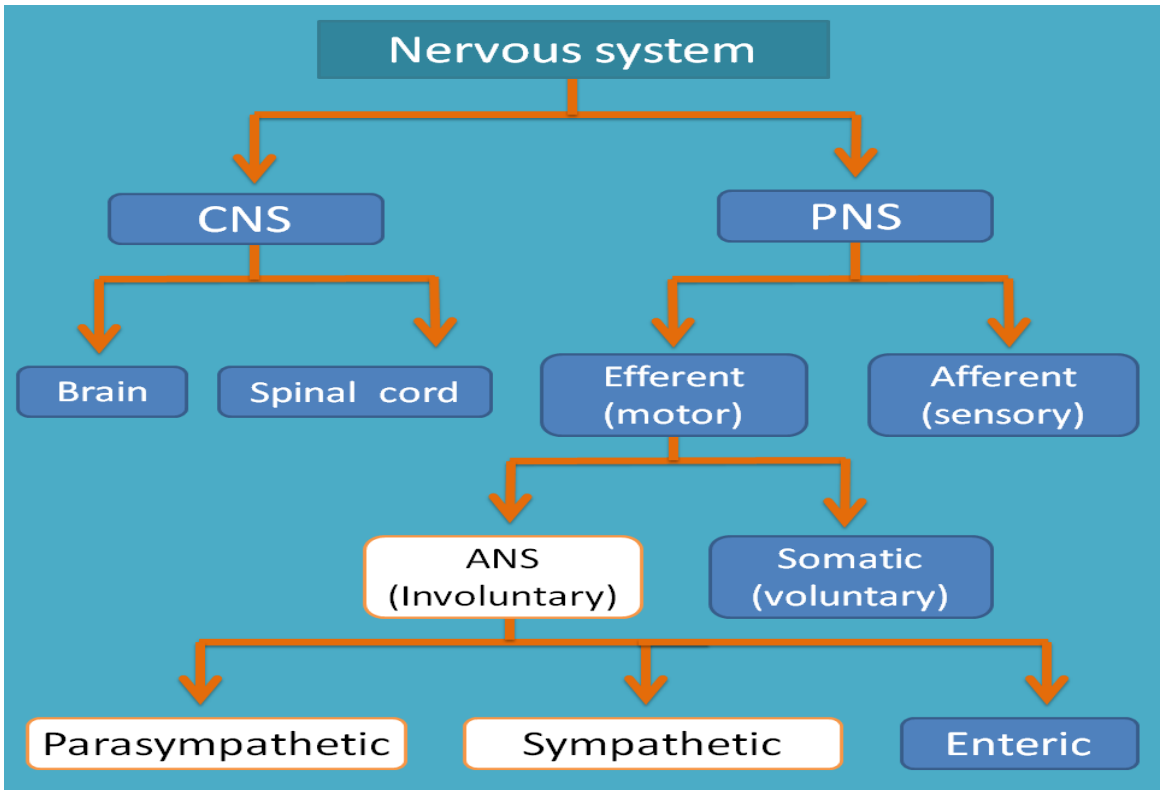
ABSTRACT

The aim of this study was to evaluate the pharmacological effects of Bisacurone on pentylenetetrazole (PTZ)-induced convulsions in laboratory mice. PTZ, a chemical convulsant, was administered to induce seizures, and Bisacurone, a compound with potential neuroprotective properties, was tested for its anticonvulsant activity. Mice were pretreated with different doses of Bisacurone, followed by PTZ administration. The onset, duration, and severity of convulsions were monitored and compared with control groups. The results indicated a dose-dependent reduction in seizure severity and delay in seizure onset with Bisacurone treatment. The compound showed significant anticonvulsant effects, suggesting its potential as a therapeutic agent for seizure disorders. Further investigations are warranted to explore its mechanism of action and safety profile. This study provides preliminary evidence for Bisacurone's neuroprotective properties, contributing to the development of new anticonvulsant therapies.

KEY WORDS: Anticonvulsants, Epilepsy, Pentylenetetrazole, Bisacurone, Swiss albino mice.

INTRODUCTION



Our bodies' control panel, the central nervous system (CNS), is made up of the brain, spinal cord, and retina. It is in charge of sensations, movement, emotions, and thought processes. More than 100 billion distinct nerve cells make up the human central nervous system (CNS), which regulates our movements, senses our environment, and shapes who we are. The system is unique in both its anatomical and physiological features, including its limited capacity for repair and its embedding in bony structures (the skull and vertebrae), which makes it difficult to access.

Definition of epilepsy

Epilepsy is a chronic neurological disorder, with a prevalence of about 1%, which is characterized by the recurrent appearance of spontaneous seizures due to neuronal hyperactivity in the brain

In 2005, a Task Force of the International League against Epilepsy (ILAE) formulated conceptual and operational definitions of “seizure” and “epilepsy”

Causes of epilepsy

The diagnosis of epilepsy usually requires that the seizures occur spontaneously. Nevertheless, certain epilepsy syndromes require particular precipitants or triggers for seizures to occur. These are termed reflex epilepsy. For example, patients with primary reading epilepsy have seizures triggered by reading. Photosensitive epilepsy can be limited to seizures triggered by flashing lights. Other precipitants can trigger an epileptic seizure in patients who otherwise would be susceptible to spontaneous seizures. For example, children with childhood absence epilepsy may be susceptible to hyperventilation. In fact, flashing lights and hyperventilation are activating procedures used in clinical EEG to help trigger seizures to aid diagnosis.

Epidemiology of epilepsy

Epilepsy is clinically similar in developing and developed countries, but the extent to which patients with epilepsy are recognized, investigated, and managed is different. Epidemiology, etiology, socio cultural, and economic factors all contribute to these differences. India is a country with diverse socioeconomic groupings.

Pathophysiology of epilepsy

Epileptic seizures arise from an excessively synchronous and sustained discharge of a group of neurons. The single feature of all epileptic syndromes is a persistent increase of neuronal excitability. Abnormal cellular discharges may be associated with a variety of causative factors such as trauma, oxygen deprivation, tumors, infection, and metabolic derangements. However, no specific causative factors are found in about half of the patients suffering from epilepsy.

GABA

GABA levels have been shown to be reduced in the cerebrospinal fluid (CSF) of patients with certain kinds of epilepsy, such as infantile spasms and untreated generalized tonic-clonic seizures, and in excised epileptic tissue from patients with drug-resistant epilepsy, suggesting that these patients have decreased inhibition.

LITERATURE REVIEW:

Test drug:

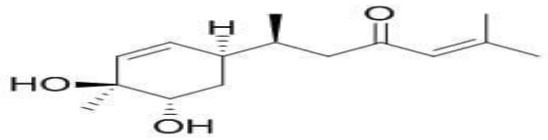
Name of test drug: Bisacurone

Bisacurone has been isolated from turmeric (curcuma longa).

Curcuma longa:

Fig.1[https://images.app.goo.gl/8fw1RpKbFEYsHfNE9]

Fig.2[https://images.app.goo.gl/uk66j2Yi25UxmFEc7]



Structure of Bisacurone

Categories: Anti-Convulsants

Solubility: Freely soluble in water, sparingly soluble in alcohol and Methanol.

Uses: Bisacurone is a bioactive terpenoid found in small amounts in turmeric that possesses anti-inflammatory and antioxidant properties. The present study focuses on the potential protective effects of bisacurone against DN via reducing renal inflammation, oxidative stress, and apoptosis.

Mechanism of Action: Bisacurone treatment reduced oxidative stress by decreasing malondialdehyde levels while enhancing antioxidant defenses through superoxide dismutase, catalase and glutathisone peroxidase levels.

Reported activity:

1) Antidiabetic
2) Suppresses hepatic lipid accumulation
3) Anti-inflammatory and anticancer activity:

MATERIAL AND METHODS

Materials:

Animals:

Swiss albino mice weighing 18-22 gm.

Instruments Used

Animal weighing electronic balance

Actophotometer

Methods:

1) Body weight

Mice were weighed daily using animal weighing balance.

2) Determination of tonic-clonic convulsions

The convulsive behavior of each mice for onset and duration of clonic and tonic seizures was observed for 30 min for signs of neurological deficits, especially hind-limb tonic seizures or convulsions, and the resultant seizures were scored as follows:

- unresponsiveness = 0
- mild contractions = 1
- clonic seizures = 2
- tonic seizures = 3 (forelimb and then hindlimb rigidly extended to rear)
- death = 4

Mice experiencing lethal convulsions were excluded from the study. Mice that exhibited at least three consecutive stage 4 or stage 5 seizures were considered convulsed, and used in this study

3) Locomotor activity:

The animal locomotor behavior was monitored using Actophotometer. Actophotometer provided with a digital counter, photocell and a light source were used to measure locomotor activity (horizontal movement) of animals.

Each animal was placed in Actophotometer for 5 minutes and basal activity score was recorded for all animals.

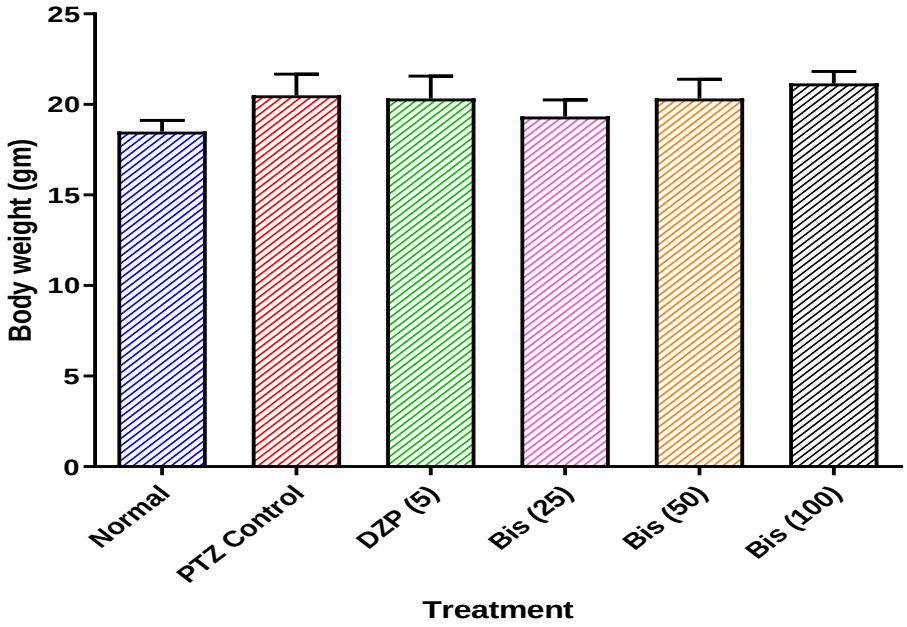
Each animal was treated with respective drug and activity score was recorded after 30 min and 1hr.

Deceased activity score was taken as index of CNS depression.

RESULTS:

1. Effect of bisacurone on body weight:

Body weight (gm) Mean ± SEM					
Normal	**PTZ control**	**Diazepam (5 mg/kg)**	**Bisacurone (25 µg/kg)**	**Bisacurone (50 µg/kg)**	**Bisacurone (100 µg/kg)**
18.50 ± 0.62	20.50 ± 1.18	20.33 ± 1.23	19.33 ± 0.92	20.33 ± 1.05	21.17 ± 0.65



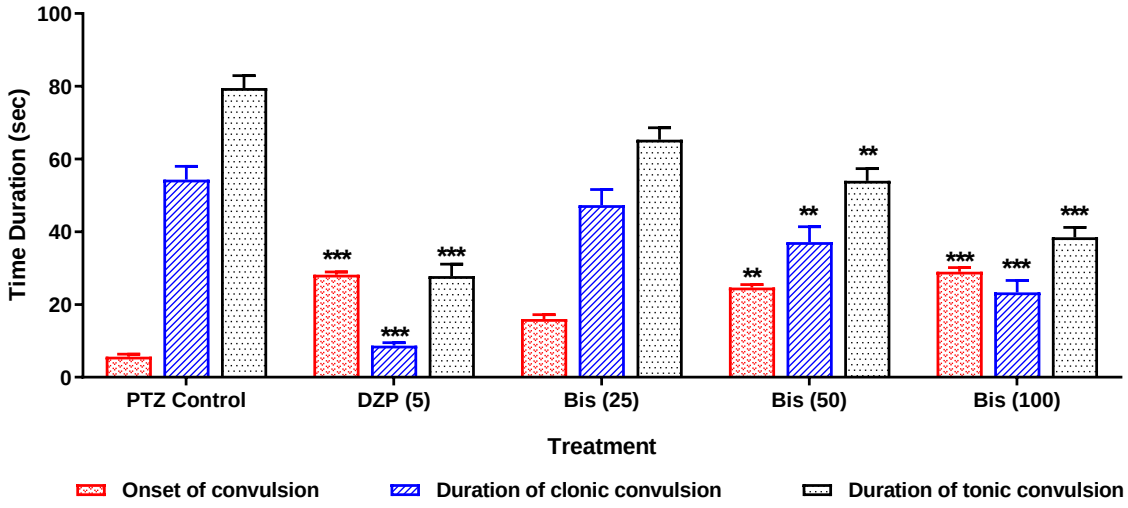
Graphical representation of effect of bisacurone on body weight

Data were analyzed by One-Way ANOVA followed by Dunnett's test.

Body weight did not differ significantly in PTZ control rats compared to normal rats. There was no significant difference in the body weight of PTZ control rats post administration of PTZ compared with normal rats. Body weight of diazepam (5 mg/kg, p.o) and bisacurone (25, 50 and 100 µg/kg, p.o.) treated group also did not differ markedly.

2. Effect of bisacurone on onset and duration of convulsion in PTZ-induced epilepsy:

Parameter	Onset and duration of convulsion Mean ± SEM					
	Normal	PTZ control	Diazepam (5 mg/kg)	Bisacurone (25 µg/kg)	Bisacurone (50 µg/kg)	Bisacurone (100 µg/kg)
Onset of convulsion	---	5.67 ± 0.67	28.17 ± 0.79***	16.00 ± 1.18	24.67 ± 0.80**	29.00 ± 1.13***
Duration of clonic	---	54.33 ± 3.64	8.67 ± 0.84***	47.33 ± 4.27	37.17 ± 4.21**	23.33 ± 3.27***
Duration of tonic	---	79.50 ± 3.45	27.83 ± 3.23***	65.33 ± 3.26	54.00 ± 3.36**	38.50 ± 2.69***



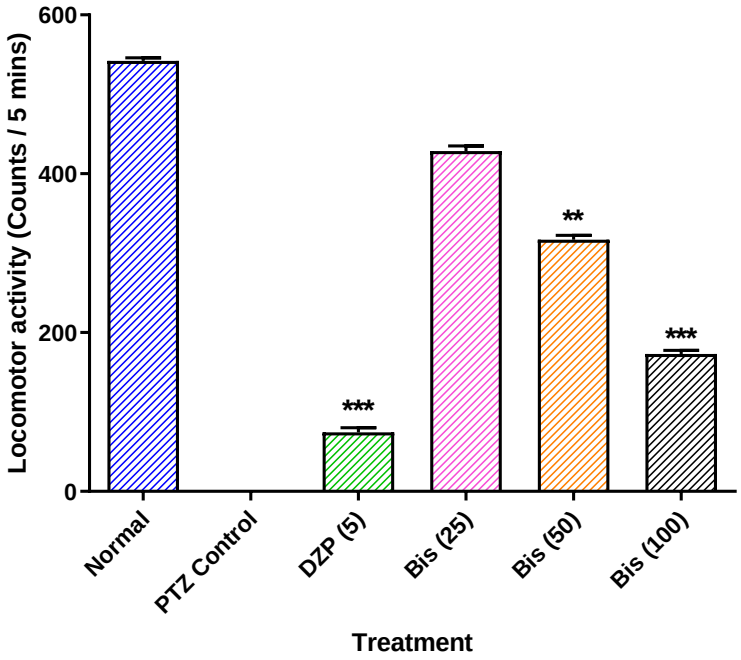
Graphical representation of effect of bisacurone on onset and duration of convulsion in PTZ-induced epilepsy.

Data were analyzed by one-way ANOVA followed by Dunnett's test $^{**}P < 0.01$ and $^{***}P < 0.001$ compared to the PTZ control group.

Onset of convulsion after diazepam (5 mg/kg, $P < 0.001$) and bisacurone (50 and 100 µg/kg, $P < 0.01$ and $P < 0.001$) administration was significantly increased than PTZ control rats. Treatment with diazepam (5 mg/kg) caused a significant decrease ($P < 0.001$) in the duration of clonic-tonic convulsion as compared to PTZ control rats. Bisacurone (50 and 100 µg/kg) administration also showed a significant and dose dependant decrease ($P < 0.01$ and $P < 0.001$) in the duration of clonic-tonic convulsion as compared to PTZ control rats. Administration of bisacurone (25 µg/kg) did not show any attenuation of onset of convulsion and duration of clonic-tonic convulsion compared to the PTZ control group.

3. Effect of bisacurone on locomotor activity during PTZ-induced post-ictal depression:

Locomotor activity (Counts / 5 mins) Mean ± SEM					
Normal	**PTZ control**	**Diazepam (5 mg/kg)**	**Bisacurone (25 µg/kg)**	**Bisacurone (50 µg/kg)**	**Bisacurone (100 µg/kg)**
542.00 ± 3.86	--	74.33 ± 5.71***	428.50 ± 6.42	316.80 ± 5.59**	173.00 ± 4.56***



Graphical representation of effect of bisacurone on locomotor activity during PTZ-induced post-ictal depression

Data were analyzed by one-way ANOVA followed by Dunnett's test. $^{**}P < 0.01$ and $^{***}P < 0.001$ compared with normal group.

Administration of diazepam (5 mg/kg, p.o.) showed significant ($P < 0.001$) decreased in locomotor activity than normal group. Bisacurone (50 and 100 µg/kg, p.o.) treatment also showed the considerable reduction in locomotor activity ($P < 0.01$, and $P < 0.001$) compared to normal rats. The treatment of bisacurone (25 µg/kg, p.o.) also showed decreased locomotor activity compared to normal rats but it was non-significant.

CONCLUSION:

Bisacurone is bioactive compound exhibit notable pharmacological activities that have attracted the interest of numerous researchers having antioxidant activity, Suppresses hepatic lipid accumulation, Antidiabetic, Anti-inflammatory, antioxidant and angiogenic activity, anticancer activity. Bisacurone was selected based on literature search and survey. The ex vivo study revealed bisacurone was effective like diazepam (standard) as a anticonvulsant agent , by increasing brain GABA level, by increasing Dopamine level, also increases serotonin level, by increasing SOD and GSH level,by decreasing MDA and nitric oxide level and and by increasing Na+K+ATPase level.

REFERENCES:

1. Acharya J N. Recent advances in epileptogenesis. CurrSci 2002; 82:10
2. Aycicek A, Iscan A. The effects of carbamazepine, valproic acid and phenobarbital on the oxidative and antioxidative balance in epileptic children. Eur. Neurol. 2006; 57(2): 65-69.
3. Ghani A, Salam A. "Changes in γ-aminobutyric acid during different stages of picrotoxin-induced seizure, and the effect of pretreatment withγ-acetylenic GABA and phenobarbital." Journal of Biosciences 1989: 14(1) 63-67
4. Babu T D and Paddikkala J. DNA fragmentation in Ehrlich Ascites tumour cells by extract of herbal plant Centella asiatica (L.). Amala Res. Bull 1994; 14: 52-56.
5. Bagdy G, Kecskemeti V, Riba P, Jakus R. Serotonin and epilepsy. Journal of neurochemistry 2007; 100(4): 857- 873
6. Babu T D, Kuttan G and Padikkala J. Cytotoxic and anti- tumour properties of certain taxa of Umbelliferae with special reference to Centella asiatica (L.) Urban, J.Ethnopharmacol 1995; (1): 53-57.
7. Blanchet P, Frommer GP. Mood change preceding epileptic seizures. J Nerv Ment Dis. 1986;174:471–476.
8. Bonting S L. Na-K activated adenosinetriphosphatase and active cation transport in the lens.Invest ophthalmol 1965; 4: 723-44
9. Bharucha N. Epidemiology of Epilepsy in India.Epilepsia 2003; 44 (1): 9–11.
10. Bradwejn J, Zhou Y, Kosyzycki D. A double-blind, placebo-controlled study on the effects of Gotu kola on acoustic startle response in healthy subjects. J. Clin. Psychopharmacol 2000; 20: 680-684.
11. Bigal M E, Lipton R B, Cohen J, & Silberstein S D. Epilepsy and migraine. Epilepsy & Behavior 2003; 4: 13- 24
12. Contó MB, de Carvalho JG, Benedito MA. Behavioral differences between subgroups of rats with high and low threshold to clonic convulsions induced by DMCM, a benzodiazepine inverse agonist. Pharmacol Biochem Behav 2005; 82(3): 417-26.
13. Cheng C L, Koo M W. Effects of Centella asiatica on ethanol induced gastric mucosal lesions in Rats. Life science 2000; 67(21): 2647- 53
14. Chatterjee T K, Chakraborty A, Pathak M, Sengupta G C. Effects of plant extract of Centella asiatica (Linn.) on cold restraint stress ulcer in rats. Indian J. Exp Biol 1962; 30(10): 889-891.

15. Chauhan P K, Pandey I P and Dhatwalia V N. Evaluation of the Anti-diabetic Effect of Ethanolic and Methanolic Extracts of Centella asiatica Leaves extract on Alloxan Induced Diabetic Rats. Advances in Biological Research 2010; 4(1): 27-30.

16. Cesarone M R, Incandela L, De Sanctis M T. Flight microangiopathy in mediumto long-distance flights: prevention of edema and microcirculation alterations with total triterpenic fraction of Centella asiatica. Angiology 2001; 52: 33-37.

17. Cesarone M R, Belcaro G, De Sanctis M T. Effects of the total triterpenic fraction of Centella asiatica in venous hypertensive micro angiopathy: a prospective, placebo-controlled, randomized trial. Angiology 2001; 52: S15- S18.

18. Clifford J, Tighe O, Croke D, Kinsella A, Sibley D Conservationofbehavioural topography to dopamine D1- likereceptor agonist sinmutant mice lacking the D1A receptor implicates a D1-like receptor not coupled to adenylyl cyclase. Neuroscience 1993; 4522(99): 1483– 1489.

19. Coimbra NC, Castro-Souza C, Segato EN, Nora JE, Herrero CF, Tedeschi-Filho W, et al. Post-ictal analgesia: involvement of opioid, serotoninergic and cholinergic mechanisms. Brain Research 2001; 888(2): 314–320.

20. Cesarone M R, Incandel L, De Sanctis M T. Evaluation of treatment of diabetic microangiopathy with total triterpenic fraction of Centella asiatica: a clinical prospective randomized trial with a microcirculatory model. Angiology 2001; 52: 49-54.

21. Dell J L. Social dimensions of epilepsy: stigma and response. In: Whitman S, Hermann BP, eds. Psychopathology in epilepsy: social dimensions 1986: 185-210.

22. Dattner A M. From medical herbalism to phytotherapy in dermatology: back to future. Dermatol Ther 2003;16(2): 106-113.

23. De Scantids M T. Treattment of edema and capillary fragility and venomous hypertension with total triterpenoid fraction of Centella asiatica: a clinical prospective placebo controlled randomized dose ranging trial 2001; 52(2): 55-59.

24. De Freitas R L, de Oliveira R C, de Carvalho A D, Felippotti T T, Bassi G S, Elias-Filho D H. et al. Role of muscarinic and nicotinic cholinergic receptors in an experimental model of epilepsy-induced analgesia. Pharmacol Biochem Behav 2004; 79(2): 367-76.

25. Dhar M L, Dhar M M, Dhawan B N, Mehrotra B N and Ray C. Screening of plants for biological activity. Indian J. Exp. Biol 1968; 6(4): 232-247.