OPEN ACCESS
Global Journal of Research in Dental Sciences
ISSN: 2583-2840 (Online)
Volume 04 | Issue 06 | Nov. – Dec. | 2024
Journal homepage: https://gjrpublication.com/gjrds/
Research Article

Analysis of Anticonvulsive Benefit of Dibenzylidene Derivative; 2, 6 (4-Dimethylaminophenyl) Methylidene Cyclohexan-1-One) In Wistar Rat Model of PTZ - Induced Seizure

Joffa, P.P.K.[1], Erigbali P.P. [1], Ezekiel A. [1] & OKOKO V.O.[1]

[1]Department of Human Physiology, Niger Delta University.

DOI: 10.5281/zenodo.14350444 **Submission Date: 21 Oct. 2024 | Published Date: 10 Dec. 2024**

***Corresponding author: Joffa, P.P.K.**
Department of Human Physiology, Niger Delta University.

Abstract

This study was designed using pentylenetetrazol - induced seizure in rats to assess the attenuating effect of a derivative of Dibenzylidene (designated as D2) on convulsive behaviour. Twenty-five (25) Wistar rat weighing about 100-280g were randomly divided into five groups; Group 1 was the control group, group two, three and four were given D2 as pretreatment while group five was given diazepam which served as the standard. The solutions were given according to the calculation of the weight of the rat and stock of the drug to get the dosage. After one hour of pretreatment the pentelenetetrazol (PTZ) solution was given to each of the five groups by intraperitoneal route to induce seizure and observed keenly for convulsive behaviours. The results showed that longer time was required for the onset of seizure in D2 administered rats compared to the control group which was not pretreated. Also group one recorded more death than the other groups. It may be inferred from the observation that D2 can be beneficial in reducing seizure severity and duration in Wistar rat.

Keywords: *seizure, Dibenzylidene derivative, PTZ, anticonvulsive.*

INTRODUCTION

Seizure is a sudden and uncontrolled electrical disturbance in the brain that can cause changes in the behavioral movements' sensation or consciousness. It is a neurological event characterized by abnormal excessive or synchronous neuronal activity. The definition of seizure aligns with the international league against epilepsy (ILEA) which defines seizure as a transient occurrence of signs and symptoms due to abnormal excessive or synchronous neuronal activity in the brain. (Fisher *et al.,* 2014). Seizure has been linked with a reduction in personal independence and autonomy alongside treatment related problems and overall reduced life expectancy (Giovangoli *et al.,* 2009; Kaplan *et al.,* 2007; Strzelczyk et al., 2022), with about one- third of patient remaining resistant to antiseizure medications which may lead to treatment discontinuation and further deterioration of quality of life (Dwiveda *et al.,* 2022; Kerr *et al.,* 2012).

Antiseizure drugs are the mainstay of treatment for epilepsy and other seizure disorder but their efficacy is limited in some patient and they may also be associated with adverse effects.

Dibenzylidene analogues are a class of compounds that have shown promising effect in the treatment of epilepsy due to their ability to modulate neuronal excitability and inhibit seizure activity; for instance, E-2, 4-dihydroxy-5-(1, 2, 3, 4-tetrahydro-2-naphthylmethylene) phenyl-2-bromoide (STX209), also known as arbaclofen reported to have anticonvulsant properties in animal and human models (Jóźwiak et al., 2019; Rogawki *et al.,* 2004). Similarly, E-2, 6-dibromobenzylidene acetone (DBA), was effective as anticonvulsant agent (Li *et al*, 2019). Their mechanisms of action as conventional anticonvulsants suppress excessive neuronal firings and its spread within the brain during seizure (Starkowski *et al.,* 1998; Mclean *et al.,* 1986). Although some uncertainty in glutamate and Gama amino butyric acid mediated responses are of concern, requiring more investigations and propective anticonvulsant regimen with good efficacy, fewer toxic effects, better tolerability, and without need for blood level monitoring (Rogawki *et al.,* 2004).

In view of this, the present investigation focused on 2, 6 (4-DIMETHYLAMINOPHENYL) METHYLIDENE] CYCLOHEXAN-1-ONE), which is a dibenzylidene derivative designated D2; with specific objective of assessing its anticonvulsive impact in rat model of PTZ – induced Seizure.

METHODOLOGY

Adult wistar rat, sample size of twenty-five (25), weight ranges from 92-280kg were procured from the department of pharmacology at Niger Delta University Bayelsa state Nigeria. The number of groups was five (5) with five rats each. Rats were fed with pelletized growers feed and water was supplied as often as necessary. The animals were kept in the plastic cages with little access in a regulated environment of (20-23 degree Celsius) under a 12 hours light /day cycle and also adequate ventilation for the purpose of acclimatization which took two weeks. Housing, handling and experimental procedure complied with recommendation and regulation set forth by national institute of health guide for care and laboratory animals (NIH publication No.8023 revised 1996) and the institutional committees for the care and use of laboratory animals of the Faculty of Basic medical sciences.

The D2 analogue is one of the analogues of dibenzylidene use to test for antiseizure in a rat model. The beaker is being weighed with the dibenzylidene solution inside it the weight is been recorded after which the substance is being dissolved by 3ml of distilled water and mixed thoroughly, if the substance is not soluble enough a drop of DMSO is been added and mixed thoroughly until the solution would dissolve and then a 7ml of water is being poured with a 10ml syringe and mixed properly till the solution become soluble for administration. After which the substance is mixed very well it is given to the Wistar rat through a gavage orally in different milliliter due to calculation of the weight of the rat. The duration for the drug is one hour before administration of diazepam solution. After which the D2 analogue is given to the rat orally the diazepam is been given to each of the rat in group 5 known as the standard. The diazepam drug is given intraperitoneal to the Wister rat after then the Wister rat are brought back to their plastic labelled cage and then a dry beaker is placed on the weighing balance and recorded. The weight of the beaker is subtracted from the weight of pentylenetetrazol salt solution to get the ml of water for disolvation, after which 20ml of water is poured into the pentylenetetrazol salt solution it is mixed thoroughly until it dissolves then it is administered intraperitoneal by a needle syringe in which it would circulate around tissues and organs of the body to cause excessive neuronal firing to the brain. The time noted for this procedure is 1-30 minutes to see if seizure would occur on Wistar rat there would be signs of hallucination, jerking and also scratching their feet on the table tile of the lab with a backward movement and stretching of hands and legs (tonic seizure) for the t3 in group 4 due to excessive firing of neurons in the brain.

RESULT ANALYSIS

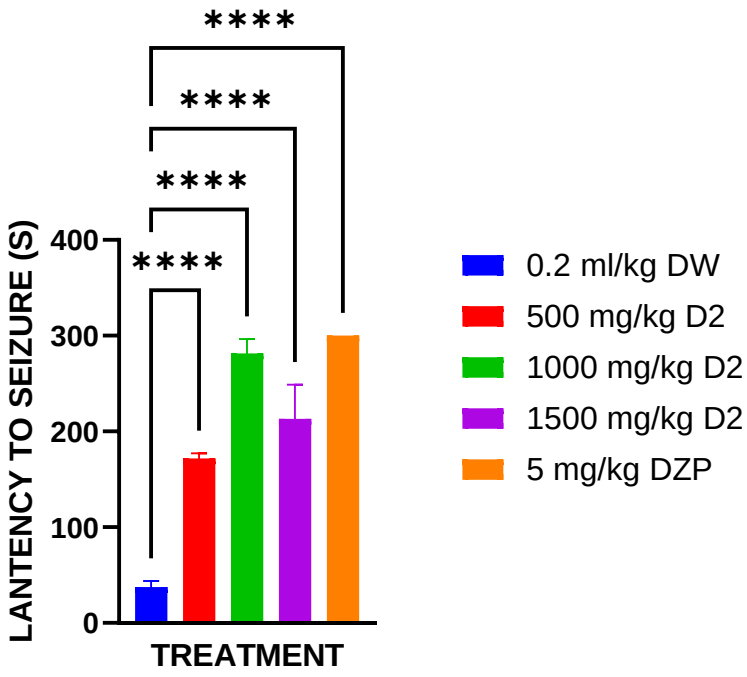

FIGURE 1: D2. Showed Statistically Significant increase**** =P<0.05 (in all test doses of the treatment), When Compared with Control Group DW=Distilled Water. D2= Dibenzylidene analog, DZP= Diazepam.

FREQUENCY

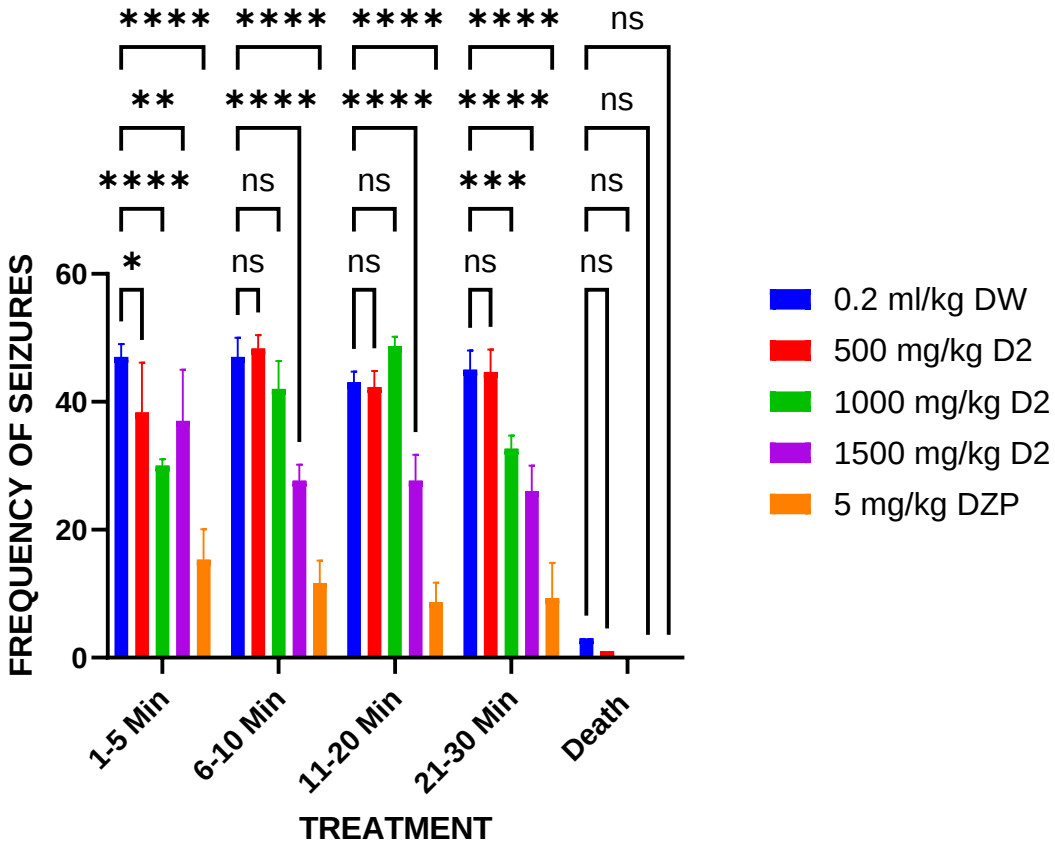

FIGURE 2: showing the frequency of seizure from 1-30 minutes in each of the four groups that was treated with d2 when compared to the control group, DW= Distilled water, D2=Dibenzylidene analogue, DPZ= diazepam

STATISTICAL ANALYSIS

The statistical analysis was designed using graphical pad prism version 10.2 (SPSS).

DISCUSSION

The study aimed to evaluate the antiseizure activities of the dibenzylidene derivative (D2) in an experimental Wistar rat model. The results demonstrated a statistically significant increase in latency to seizure and a significant reduction in seizure frequency across all test doses of D2 when compared to the control group treated with distilled water (DW). These findings were compared against diazepam (DZP), a well-known anticonvulsant, which served as the positive control.

LATENCY TO SEIZURE

The latency to seizure, as shown in Figure 1, indicates the time taken for seizures to commence after the administration of treatments. All doses of D2 (500 mg/kg, 1000 mg/kg, and 1500 mg/kg) exhibited a highly significant ($P<0.05$) increase in latency to seizure when compared to the control group. This suggests that D2 effectively delays the onset of seizures, providing a potential therapeutic benefit in seizure management. The increase in latency was comparable to the effect observed with 5 mg/kg DZP, implying that D2 could be as effective as DZP in delaying seizure onset.

FREQUENCY OF SEIZURES

The figure 2 illustrates the frequency of seizures over a 30-minute observation period for each treatment group. The frequency of seizures was significantly reduced in all D2-treated groups compared to the control. Specifically, the highest dose of D2 (1500 mg/kg) demonstrated the most substantial reduction in seizure frequency, followed closely by 1000 mg/kg and 500 mg/kg doses. The statistical significance of these reductions was indicated by $P<0.05$ in most instances, suggestive of robust antiseizure activity of D2.

COMPARATIVE ANALYSIS WITH DIAZEPAM

When comparing the antiseizure effects of D2 with DZP, D2 at 1500 mg/kg and 1000 mg/kg exhibited comparable efficacy to 5 mg/kg DZP in both increasing latency and reducing seizure frequency. This comparison underscores the potential of D2 as an effective anticonvulsant agent. The lower dose of D2 (500 mg/kg) also showed significant antiseizure activity but was slightly less effective than the higher doses, indicating a dose-dependent response.

CONCLUSION

The finding from this study indicates antiseizure potential of dibenzylidene derivative (D2) exhibited in a dose-dependent manner. These effects were comparable to those of diazepam, suggesting that D2 could serve as a promising alternative or adjunctive treatment for seizure management. Further studies are to explore the underlying mechanisms of D2 antiseizure activity and its potential clinical applications in human subjects may be desirable.

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CITATION

Joffa, P.P.K., Erigbali P.P., Ezekiel A., & OKOKO V.O. (2024). Analysis of Anticonvulsive Benefit of Dibenzylidene Derivative; 2, 6 (4-Dimethylaminophenyl) Methylidene Cyclohexan-1-One) In Wistar Rat Model of PTZ - Induced Seizure. In Global Journal of Research in Dental Sciences (Vol. 4, Number 6, pp. 7–10). https://doi.org/10.5281/zenodo.14350444