Trop J Nat Prod Res, April 2023; 7(4):2811-2816 **ISSN 2616-0684 (Print)**
ISSN 2616-0692 (Electronic)

Tropical Journal of Natural Product Research

Available online at https://www.tjnpr.org

Original Research Article

The Synergistic Effect of Fluoxetine, Buspirone, and Sumatriptan with Sodium Valproate and Phenobarbitone in Experimental Models of Convulsion

Abigail M. Akhigbemen[a]*, Enoch E. Akamu[a], Isreal O. Bolanle [a]

[a]*Department of Pharmacology & Toxicology, Faculty of Pharmacy, University of Benin, Benin- City 300001, Nigeria*

ARTICLE INFO

Article history:
Received 15 February 2023
Revised 31 March 2023
Accepted 04 April 2023
Published online 01 May 2023

ABSTRACT

Epilepsy is one of the most common brain disorders, affecting at least 50 million persons worldwide. Antiepileptic's have several dose-dependent side effects, necessitating a dose reduction or addition of an adjunct therapy. This study investigates the anticonvulsant activity of low dose phenobarbitone and sodium valproate when combined with buspirone, sumatriptan and fluoxetine. Mice were randomly divided into five groups; group I were treated with 0.2 ml of distilled water, group II were administered 20 mg/kg fluoxetine and 150 mg/kg sodium valproate, group III were administered 20 mg/kg sumatriptan and 150 mg/kg sodium valproate, group IV were administered 5 mg/kg buspirone and 150 mg/kg sodium valproate while group V were administered 150mg/kg of sodium valproate. One hour later, 70 mg/kg pentylenetetrazole (PTZ) was intraperitoneally administered to all mice. The onset of central nervous system (CNS) activity and percentage protection were recorded. The above was repeated using phenobarbitone (15 mg/kg). For strychnine (STN)-induced convulsion, the procedure was repeated with 1 mg/kg strychnine used in place of PTZ. For maximal electroshock shock -induced convulsion, mice were subjected to electroshock current of 50 mA for 0.2 seconds after one hour of administering the drugs as done in the other methods. Sumatriptan and sodium valproate combination significantly delayed the onset of CNS activity when compared with the negative control ($p<0.05$) in PTZ-induced convulsion. Fluoxetine and buspirone in combination with sodium valproate significantly delayed the onset of CNS activity ($p<0.0001$) against STN-induced convulsion. The different drugs in combination with phenobarbitone protected the mice against MES and PTZ-induced convulsion.

Keywords: Anticonvulsants, serotonergic drugs, animal models, fluoxetine, depression..

Introduction

Epilepsy is a non-communicable neurological disease that affects individuals irrespective of their ages, races, social classes, and geographical locations. [1] Epilepsy is classified into three kinds based on etiology; it includes acquired, idiopathic, and epilepsy of genetic or developmental origin. The incidence of epilepsy is higher in at the two extremes of life (the very young and old). [2] Children have the highest incidence of epilepsy by the end of their first year of life, which then declines up until they become adults.[3] The prevalence of epilepsy is highest among kids in low to middle-income countries LMIC; this may be due to the under diagnosis of the ailment. Because epilepsy involves more than just spontaneous recurring seizures, it should be viewed as a spectrum condition. Epilepsy occurs as a comorbid condition, occurring with behavioral and psychological problems including depression, anxiety, learning difficulties, attention-deficit hyperactivity disorder, cognitive impairment, as well as autism.[4] The most prevalent psychiatric co-morbidity being depression, is interestingly linked to limbic and hippocampal impairment, two brain regions that cause seizures.[5]

*Corresponding author. E mail: abigail.omo-isibor@uniben.edu
Tel: +234-703-247-0846

Citation: Akhigbemen AM, Akamu EE, Bolanle IO. The Synergistic Effect of Fluoxetine, Buspirone, and Sumatriptan With Sodium Valproate and Phenobarbitone in Experimental Models of Convulsion. Trop J Nat Prod Res. 2023; 7(4):2811-2916 http://www.doi.org/10.26538/tjnpr/v7i4.24

Official Journal of Natural Product Research Group, Faculty of Pharmacy, University of Benin, Benin City, Nigeria.

Epileptic patients who are depressed are more commonly refractory, and individuals suffering from epilepsy are more likely to have depression; shows a research on the relationship between these two conditions.[5]

Adverse effects are commonly noticed at doses (and serum concentrations) within the prescribed range because Antiepileptic drugs (AEDs) have a narrow therapeutic window. The ideal management strategy for epilepsy, frequently entails striking a balance between the need to provide comprehensive symptom control and the requirement to reduce toxicity.[6]Slow dosage titration is advised while using some AEDs since some adverse effects can be reduced or completely avoided by introducing the drug gradually.[7] This applies to both idiosyncratic reactions like skin rashes, as in the cases of Carbamazepine, Phenytoin, and Lamotrigine, as well as CNS side effects, as in the cases of topiramate, tiagabine, and many other drugs.[7,8]

Bonnycastle *et al*,[9] first proposed in 1957 that there could be a connection between serotonin (5-HT) and the prevention of epilepsy. In their research, they showed that several anticonvulsants, including phenytoin, increased the levels of serotonin in the brain. Serotonergic neurotransmission influences several experimentally induced seizures and is thought to contribute to the increased susceptibility to seizures as observed in rodents with genetic epilepsy. [10-16] Both focal (limbic) and generalized seizures are often prevented by substances that increase extracellular levels of serotonin , such as 5-hydroxytryptophan and 5-HT reuptake blockers.[17-19] Moreover, a decrease in brain 5-HT decreases the threshold for convulsions that are induced by sound, chemicals, or electricity.[20-21]

Using micro dialysis in genetically epileptic prone rats (GEPR), [22] the impact of anti-epileptic medications on serotonin was assessed.[22] Anti-epileptics enhanced extracellular levels of 5-HT concentrations in GEPRs as well as a dose-related anticonvulsant effect[22] Using micro

dialysis, the impact of anticonvulsant therapy with phenytoin, lamotrigine, and carbamazepine (CBZ) on baseline and stimulated extracellular levels of dopamine (DA) and 5-hydroxytryptamine (5-HT) in the hippocampus of freely moving rats was investigated. [23] Their research showed that the concentration of extracellular transmitters affected the impact of antiepileptic medications on 5-HT release concentrations of transmitters.

Considering these known findings, this study therefore sought to evaluate the synergistic potential of fluoxetine, buspirone and sumatriptan in combination with low dose of sodium valproate and phenobarbitone in mice models of convulsion.

Methods

Animals

Mice of both sexes weighing about 21.3 g – 34.0 g were used in this study. They were obtained from the animal house located in the Department of Pharmacology, Faculty of Pharmacy, University of Benin, Benin city. The animals were allowed free access to water and ordinary animal pellets. Ethical approval (EC/FP/22/08) for the use of animals was obtained from the institution's committee.

Drugs and chemicals

All drug used were of analytical grade and obtained from reputable suppliers. They were solubilized in distilled water and freshly prepared before every experiment.

Pentylenetetrazol (PTZ)-induced convulsion

Twenty (20) mice were used; they were split into five groups of 4 mice each. Mice in group I were treated with 0.2 ml of distilled water as negative control, group II mice were administered 20 mg/kg and 150 mg/kg of fluoxetine and sodium valproate respectively, group III mice were administered 20 mg/kg and 150 mg/kg of sumatriptan and sodium valproate respectively. Also group IV mice were administered 5 mg/kg and 150 mg/kg of buspirone and sodium valproate respectively while group V were administered 150 mg/kg of sodium valproate as positive standard. All drugs were administered orally. An hour later, 70 mg/kg PTZ was administered intraperitoneally (i.p) to all the mice in the groups.[24] The time of PTZ administration, onset of CNS activity, and mortality protection were then recorded. The procedure was repeated using phenobarbitone (15 mg/kg) as positive standard.

Maximum electroshock seizure (MES)-induced convulsion

Twenty (20) mice were used; they were split into five groups of 4 mice each. Mice in group I were treated with 0.2 ml of distilled water as negative control, group II mice were administered 20 mg/kg and 150 mg/kg of fluoxetine and sodium valproate respectively, group III mice were administered 20 mg/kg and 150 mg/kg of sumatriptan and sodium valproate respectively, also group IV mice were administered 5 mg/kg and 150 mg/kg of buspirone and sodium valproate respectively while group V mice were administered 150 mg/kg of sodium valproate as positive standard. All drugs were administered orally. One hour later, all animals were exposed to electroshock current of 50 mA for 0.2 seconds through a pair of ear clip electrodes.[25] The onset of CNS action, and mortality protection were then recorded. The procedure was repeated using phenobarbitone (15 mg/kg) as positive standard.

Strychnine (STN)-induced convulsion

Twenty (20) mice were used; they were split into five groups of 4 mice each. Mice in group I were treated with 0.2 ml of distilled water as negative control, group II mice were administered 20 mg/kg and 150 mg/kg of fluoxetine and sodium valproate respectively, group III mice were administered 20 mg/kg and 150 mg/kg of sumatriptan and sodium valproate respectively, also group IV mice were administered 5 mg/kg and 150 mg/kg of buspirone and sodium valproate respectively while group V were administered 150 mg/kg of sodium valproate as positive standard. All drugs were co administered orally. An hour later, 1 mg/kg STN was administered intraperitoneally to all the mice in all group.[26] The time of STN administration, onset of CNS activity, and mortality protection were then recorded. The procedure was repeated using phenobarbitone (15 mg/kg) as positive standard.

Statistical analysis

Data were expressed as the mean ± standard error of the mean (S.E.M). Comparison between the treatment groups and negative control was carried out using one-way analysis of variance (ANOVA) followed by Tukey post hoc test. Analysis and data presentation were done using GraphPad Prism version 8.0.2. Results were considered significant when $P < 0.05$.

Results and Discussion

Effect of fluoxetine, Sumatriptan, and Buspirone in combination with sodium valproate on PTZ-induced convulsion in mice.

Figure 1 shows that Sumatriptan (SU) and Sodium valproate (NA) combination (NA+SU) significantly delayed the onset of convulsion when compared with the negative control group (P<0.05). There was a noticeable delay in the onset of CNS activity with the NA+FTX and NA+BU combinations; however, this delay was not significant when compared with control (Figure 1). Whereas the different drug combinations and positive standard all showed protection in varying degrees against PTZ-induced convulsion as seen in Table 1.

This shows that sumatriptan potentiates the effect of sodium valproate when co-administered. Sumatriptan is a 5-$HT_{1B/D}$ receptor agonist which was merely thought to act peripherally but has been discovered to also act at the central locations including the substantial extracellular levels of the brain. [27,28] Sodium valproate is a standard anticonvulsant proposed to act through several mechanisms including eliciting activity at the voltage-sensitive Na^+ channels,[29] diminishing T-type Ca^{2+} currents in primary afferent neurons[30] and, at relatively high drug concentrations, increasing brain GABA levels and also potentiating the effect of GABA.[31]

Sodium valproate is effective against generalized tonic-clonic and partial seizures in people and against absence seizures[32] which are similar to the ones elicited by PTZ. PTZ is a known noncompetitive antagonist of $GABA_A$ receptor that acts through the t-butyl-bicyclo-phosphorothionate site of thereby decreasing its activity. [33] PTZ also has the ability to charge the potassium and calcium channel conductance.[34]

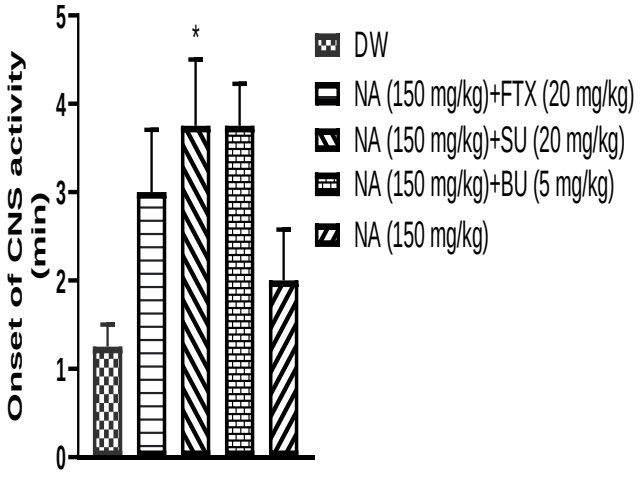

Figure 1: Effect of Fluoxetine, Sumatriptan and Buspirone in combination with Sodium valproate on PTZ-induced convulsion in mice. Data presented as Mean ± SEM, *P<0.05 versus DW group. DW - Distilled Water; NA - Sodium Valproate; FTX - Fluoxetine; SU - Sumatriptan; BU - Buspirone. n=4 mice.

Table 1: Percentage protection in mice treated with Fluoxetine, Sumatriptan, Buspirone in combination with Sodium Valproate in Pentylenetetrazole-induced convulsion.

Drugs	% Protection
DW	0
NA (150 mg/kg) + FTX (20 mg/kg)	75
NA (150 mg/kg) + SU (20 mg/kg)	25
NA (150 mg/kg) + BU (5 mg/kg)	75
NA (150 mg/kg)	50

Therefore, PTZ-induced convulsion is due to antagonism of GABAergic neurotransmission. Since Sodium valproate is effective against tonic-clonic seizure and absence seizures, it ought to totally protect the mice against PTZ-induced convulsion but only 50 % of the mice were protected. This might be due to the low dose of sodium valproate used in the study. Increase in dose of sodium valproate might likely give 100 % protection against PTZ-induced convulsion. Sodium valproate a classic anticonvulsant is known to increase baseline levels of 5-HT and possibly promotes its release.[23, 35, 36] On the other hand, buspirone is a 5-HT_{1A} receptor agonist and fluoxetine a selective serotonin reuptake inhibitor, [37, 38] suggestive that serotonin plays an significant role in epilepsy. Also, revealing that increased serotonin level in the CNS can delay or prevent the onset of epilepsy.

Effect of Fluoxetine, Sumatriptan, and Buspirone in combination with sodium valproate on STN-induced convulsion in mice

Figure 2 shows that, sodium valproate (NA), sodium valproate (NA) + buspirone (BU), and sodium valproate (NA) + sumatriptan (SU) all significantly delayed the onset of CNS activity when compared with the negative control ($p<0.001$, $p<0.0001$) respectively (Figure 2). Sodium valproate (NA) + sumatriptan (SU) combination also showed protection to the mice against STN-induced convulsion as shown in Table 2.

Strychnine is a poisonous alkaloid that works predominantly in the spinal cord as a competitive inhibitor of the postsynaptic glycine receptor. Inhibition of glycine, a principal inhibitory neurotransmitter, induces excessive activation of postsynaptic neurons, resulting in uncontrollable generalized muscular spasms.

From the result, sodium valproate significantly delayed the onset of CNS activity when compared with the negative control and also protects the mice against STN-induced convulsion, showing its effectiveness against strychnine-induced convulsion.

Effect of Fluoxetine, Sumatriptan, and Buspirone in combination with sodium valproate on MES-induced convulsion in mice

Table 3 shows that the different combinations protected the mice against MES-induced convulsion while the standard and the control did not protect the mice. For simulating generalized tonic-clonic seizures, maximum electroshock induction is often employed.

Table 2: Percentage protection in mice treated with Fluoxetine, Buspirone, Sumatriptan in combination with Sodium valproate in Strychnine-induced convulsion.

Drugs	% Protection
DW	0
NA (150mg/kg) + FTX (20mg/kg)	0
NA (150mg/kg) + SU (20mg/kg)	75
NA (150mg/kg) + BU (5mg/kg)	0
NA (150mg/kg)	100

DW - Distilled Water; NA - Sodium Valproate; FTX - Fluoxetine; SU- Sumatriptan; BU - Buspirone.% (percentage) , n = 4 mice.

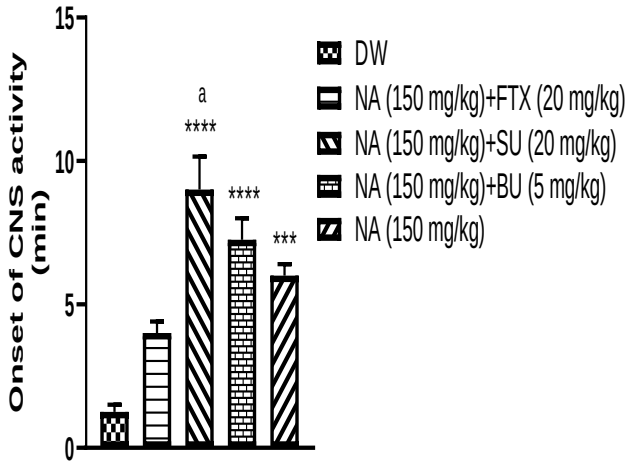

Figure 2: Effect of Fluoxetine, Sumatriptan, and Buspirone in combination with Sodium valproate on Strychnine-induced convulsion in mice. Data presented as Mean ± SEM . ***P<0.001, ****P<0.0001 versus DW group.DW- Distilled Water; NA - Sodium Valproate; FTX - Fluoxetine; SU - Sumatriptan; BU – Buspirone. n= 4 mice.

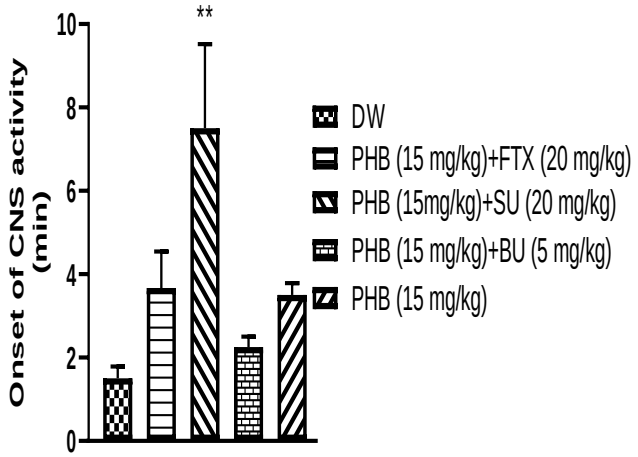

Figure 3: Effect of fluoxetine, sumatriptan, and buspirone in combination with phenobarbitone on Pentylenetetrazole-induced convulsion in mice. **p<0.01 versus DW group. DW- Distilled Water; PHB - Phenobarbitone; FTX - Fluoxetine; SU - Sumatriptan; BU- Buspirone. n=4 mice.

Table 3: Percentage protection in mice treated with Fluoxetine, Buspirone, Sumatriptan in combination with sodium valproate in Maximal electroshock -induced convulsion.

Drugs	% Protection
DW	0
NA (150 mg/kg) + FTX (20 mg/kg)	50
NA (150 mg/kg) + SU (20 mg/kg)	50
NA (150 mg/kg) + BU (5 mg/kg)	25
NA (150 mg/kg)	0

It is mostly linked to seizures of that can be produced by auricular stimulation at threshold current intensity.[40] Drugs effective against tonic-clonic generalised seizures prevent seizures induced by the MES test.[41] Sodium (Na^+) channels are modulated to cause convulsions during maximum electroshock (MES). Hence, Na^+ channel inhibitors such as phenytoin, carbamazepine, and phenobarbitone prevent MES-induced convulsions.

From the result, fluoxetine and sumatriptan combinations offered 50% protection to the mice while buspirone combination provided 25 % protection. This shows that increased serotonin levels in the brain decreases the onset of convulsion. The inhibitory neurotransmitter serotonin is released by brainstem neurons and neurons that innervate the digestive system (enteric nervous system). [42] Serotonin precursors as seen in this study inhibited the excitatory effect caused by the MES.

Effect of Fluoxetine, Sumatriptan, and Buspirone in combination with Phenobarbitone on PTZ-induced convulsion in mice.

Figure 3 showed that, combined therapy of phenobarbitone (PHB) and sumatriptan (SU) significantly delayed the onset of seizures versus the negative control (P<0.01). Other combinations showed noticeable delay in the onset of convulsion when compared with the control (Figure 3). The different combination therapies and the positive standard all protected the mice against PTZ-induced convulsion as shown in Table 4.

Phenobarbitone is a barbiturate that increases GABA levels postsynaptically via its interaction with the alpha and beta subunits of the $GABA_A$ receptor.[43] Barbiturates cause postsynaptic hyperpolarization and CNS depression via increases in chloride ion flow. $GABA_A$ receptors are affected by phenobarbital and pentobarbital in a dose-dependent manner. [44] At higher micro molar concentrations associated with anesthetic doses, these medications activate chloride channels.[44] Barbiturates and benzodiazepines both bind to $GABA_A$ receptors. Even at relatively low concentrations barbiturates activate GABA-A receptors while boosting chloride ion inflow.[45] Barbiturates such as phenobarbitone are efficacious in the kindling rat model of partial seizures and PTZ-induced clonic seizures.[32]

From the result, only sumatriptan and phenobarbitone combination considerably delayed the onset of convulsion when compared with the negative control. This shows that sumatriptan increases the effect of phenobarbitone. Table 4 shows all the combinations protecting (100 % protection) the mice against PTZ-induced convulsion.

Effect of Fluoxetine, Sumatriptan, and Buspirone in combination with Phenobarbitone on Styrchnine-induced convulsion in mice.

The different combination therapies and the positive standard PHB, all did not protect mice against STN-induced convulsion (Table 5). They all significantly delayed the onset of CNS activity (p<0.05, p<0.01, p<0.001) as seen in Figure 4.This delay can be attributed to the anticonvulsant properties of phenobarbitone. None of the mice were protected against STN-induced convulsion revealing that phenobarbital and the drugs co-administered do not antagonize STN effect (inhibiting glycine).

Effect of fFuoxetine, Sumatriptan, and Buspirone in combination with Phenobarbitone on MES-induced convulsion in mice.

Table 6 shows that the different drug combinations and the standard all protected the mice against MES-induced convulsion. This suggests that low dose phenobarbitone in combination with either serotonin agonist or reuptake inhibitors can prevent convulsion. Comparing this to sodium valproate, serotonin played a vital role in potentiating the effect of phenobarbitone; thus protecting the mice from convulsion as the rate of protection was higher compared to the sodium valproate treated group.

Conclusion

Fluoxetine, buspirone and sumatriptan all enhanced the activity of sodium valproate against PTZ-induced convulsion. Sumatriptan greatly enhanced the anticonvulsant activity of sodium valproate and phenobarbitone against STN-induced and PTZ-induced convulsion.

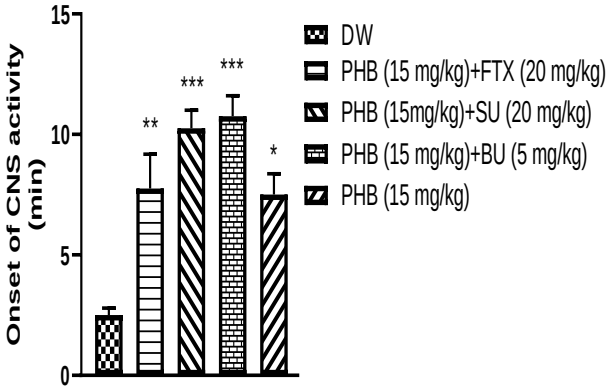

Figure 4: Effect of FTX, SU, and BU in combination with PHB on STN-induced convulsion in mice. *P<0.05, **P<0.01, ***p<0.001 versus DW. DW- Distilled Water; PHB- Phenobarbitone; FTX- Fluoxetine; SU- Sumatriptan; BU- Buspirone,

Table 4: Percentage protection in mice treated with Fluoxetine, Buspirone, Sumatriptan in combination with Phenobarbitone in Pentylenetetrazole-induced convulsion.

Drugs	% Protection
DW	0
PHB (15 mg/kg) + FTX (20 mg/kg)	100
PHB (15 mg/kg) + SU (20 mg/kg)	100
PHB (15 mg/kg) + BU (5 mg/kg)	100
PHB (15 mg/kg)	100

DW- Distilled Water; PHB- Phenobarbitone; FTX- Fluoxetine; SU- Sumatriptan; BU- Buspirone, %(percentage). n=4 per group

Table 5: Percentage protection in mice treated with fluoxetine, buspirone, sumatriptan in combination with phenobarbitone in strychnine-induced convulsion.

Drugs	% Protection
DW	0
PHB (15 mg/kg) + FTX (20 mg/kg)	0
PHB (15 mg/kg) + SU (20 mg/kg)	0
PHB (15 mg/kg) + BU (5 mg/kg)	0
PHB (15 mg/kg)	0

DW - Distilled Water; PHB - Phenobarbitone; FTX - Fluoxetine; SU - Sumatriptan; BU - Buspirone, % (percentage) n = 4 per group.

Table 6: Percentage protection in mice treated with Fluoxetine, Buspirone, Sumatriptan in combination with Phenobarbitone in Maximal electroshock induced convulsion.

Drugs	% Protection
DW	0
PHB (15 mg/kg) + FTX (20 mg/kg)	100
PHB (15 mg/kg) + SU (20 mg/kg)	100
PHB (15 mg/kg) + BU (5 mg/kg)	100
PHB (15 mg/kg)	75

DW - Distilled Water; PHB - Phenobarbitone; FTX - Fluoxetine; SU - Sumatriptan; BU – Buspirone, % (percentage). n = 4 per group

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

Acknowledgements

The authors appreciate the help and effort of Mr. Collins Osaigbovo and Mr Philip Obarisiagbon, both of the Department of Pharmacology &Toxicology, University of Benin, Benin-city.

References

1. World Health Organization (WHO). Epilepsy Fact Sheet. 2023. Available from: https://www.who.int/news-room/fact-sheets/detail/. [Accessed on 27/03/2023].
2. Beghi E. The Epidemiology of Epilepsy. Neuroepidemiology 2020; 54:185-191.
3. Camfield P, Camfield C. Incidence, prevalence and aetiology of seizures and epilepsy in children.Epileptic Disord.2015; 17(2):117–123.
4. GrzegorzewskaAM, Wiglusz MS, Landowski J, Cubała, WJ, Włodarczyk A, & Szarmach J. Multiple Comorbidity Profile of Psychiatric Disorders in Epilepsy. J. Clin. Med., 2021; 10(18), 4104.
5. Amelia JS, Louise S, Caroline H, and Milena G. Anxiety and depressive disorders in people with epilepsy:A meta-analysis. Epilepsia. 2017; 58(6):973–982, 201.
6. Perucca E, Beghi E, Dulac O, Shorvon S, Tomson T. Assessing risk to benefit ratio in antiepileptic drug therapy. Epilepsy Res. 2000; 41(2):107-39.
7. Fishman J, Kalilani L, Song Y, Swallow E, Wild I. Antiepileptic Drug Titration and Related Health Care Resource Use and Costs. J Manag Care Spec Pharm. 2018; 24(9):929-938.
8. Besag FMC. Approaches to reducing the incidence of lamotrigine-induced rash. CNS Drugs 2000; 13:21–23.
9. Bonnycastle D. D., Giarman N. J. and Paasonen M. K. Anticonvulsant compounds and 5-hydroxytryptamine in rat brain. Br. J. Pharmacol (1957); 12, 228–231.
10. Kilian M. and Frey HH. Central monoamines and convulsive thresholds in mice and rats. Neuropharmacology 1973; 12:681–692.
11. Buterbaugh CG. Effects of drugs modifying central serotonergic function on the response of extensor and non-extensor rats to maximal electroshock.1978; Life Sci. 23:2393–2904.
12. Przegalinski E. Monoamines and the pathophysiology of seizure disorders, in Handbook of Experimental Pharmacology Frey, H. H. and Janz, D., eds), 1985; pp101–137.
13. Hiramatsu M K, Kawanaga K, Kabuto H and Mori A. Reduced uptake and release of 5-hydroxytryptamine and taurine in the cerebral cortex of epileptic El mice. Epilepsy Res. 1987; 1:40–44.
14. Dailey JW, Yan QS, Mishra PK, Burger RL, Jobe PC. Effects of fluoxetine on convulsions and on brain serotonin as detected by microanalysis in genetically epilepsy prone rats. J Pharmacol Exp Ther 1992; 2:533– 540
15. Gerber K, Filakovszky J, Halasz P and Bagdy G. The 5-HT1A agonist 8-OH-DPAT increases the number of spike-wave discharges in a genetic rat model of absence epilepsy. Brain Res.1998; 807, 243–245
16. Filakovszky J, Gerber K and Bagdy G. A serotonin-1A receptor agonist and N-methyl-D-aspartate receptor antagonist oppose each other's effects in a genetic rat epilepsy model. Neurosci. Lett 1999; 261:89–92
17. Löscher W. Genetic animal models of epilepsy as a unique resource for the evaluation of anticonvulsant drugs. A review. Meth. Find. Exp. Clin. Pharmacol. 1984; 6:531–547.
18. Prendiville S, Gale K. Anticonvulsant effect of fluoxetine on focally evoked limbic motor seizures in rats. Epilepsia, 1993; 34:381–384.
19. Yan QS, Jobe PC, Cheong JH, Ko KH and Dailey JW. Role of serotonin in the anticonvulsant effect of fluoxetine in genetically epilepsy prone rats. Naunyn-Schmiedebergs Arch. Pharmacol. 1994; 350:149–152
20. Browning RA, Hoffman WE and Simonton RL. Changes in seizure susceptibility after intracerebral treatment with 5,7-dihydroxy-tryptamine: role of serotonergic neurones. Ann. N. Y. Acad. Sci. 1978; 305:437–456.
21. Statnick MA, Maring-Smith ML, Clough RW, Wang C, Dailey JW, Jobe PC and Browning RA. Effects of 5,7-dihydroxy-tryptamine on audiogenic seizures in genetically epilepsy prone rats. Life Sci.1996; 59:1763–1771.
22. Dailey JW, Reith ME, Yan QS, Li M Y and Jobe PC. Anticonvulsant doses of carbamazepine increase hippocampal extracellular serotonin in genetically epilepsy-prone rats: dose–response relationships. Neurosci. Lett 1997; 227:13–16.
23. Ahmad S, Fowler LJ and Whitton PS. Lamotrigine, carbamazepine and phenytoin differentially alter extracellular levels of 5-hydroxytryptamine, dopamine and amino acids. Epilepsy Res.2005; 63:141–149.
24. NgoBum E, Schmutz M, Meyer C, Rakotonirina A, Bopelet M. Anticonvulsant properties of the methanolic extract of Cyperus articulates (Cyperaceae). J Ethnopharmacol.2001; 76:145-150.
25. Bolanle O.I, Oviasogie OD, Owolabi OJ, Akhigbemen AM, Obarisiagbon AP, Osaigbovo AC. Evaluation of the Anti-Convulsant Activity of Aqueous Leaf Extract of Jatropha curcas (Euphorbiaceae) in Mice: Trop J. Nat Prod. Res,2018; 2(11):489–493.
26. Porter RJ, Cereghino JJ, Gladding GD. Antiepileptic drug development program. Cleve Clin1984; 51: 293-305
27. Humphrey P, Feniuk W, Marriott A, Tanner R, Jackson M, Tucker M. Preclinical studies on the anti-migraine drug, sumatriptan. European neurology 1991; 31:282- 290.
28. Johnson DE, Rollema H, Schmidt AW, McHarg AD. Serotonergic effects and extracellular brain levels of eletriptan, zolmitriptan and sumatriptan in rat brain. European journal of pharmacology2001; 425:203-210
29. White HS. Mechanisms of antiepileptic drugs. In: Porter R, Chadwick D, eds. Epilepsies II. Boston: Butterworth-Heinemann, 1997; 1-30.
30. Kelly KM, Gross RA, Macdonald RL . Valproic acid selectively reduces the low-threshold (T) calcium in rat nodose neurons. Neurosci Lett 1990; 116: 233-238.
31. Rogawski MA, Porter RJ. Antiepileptic drugs: pharmacological mechanisms and clinical efficacy with consideration of promising developmental stage compounds. Pharmacol Rev 1990; 42:223-286.
32. White SH. Comparative Anticonvulsant and Mechanistic Profile of the Established and Newer Antiepileptic Drugs. Epilepsia,1999; 4O (Suppl. 5):S2-S10.
33. Korpi ER, Grűnder G, Lűddens H. Drug interactions at GABA(A) receptors. Prog Neurobiol 2002; 67:113-159.
34. Madeja M, Stocker M, Mushoff V. Potassium current in epilepsy: effect of the epileptogenic agent pentylenetetrazole on a cloned potassium channel. Brain Research, 1994; 656:287-294.
35. Okada M., Kaneko S., Hirano T., Ishida M., Kondo T., Otani K. and Fukushima Y. Effects of zonisamide on extracellular levels of monoamine and its metabolite, and on

Ca^{2+}-dependent dopamine release. Epilepsy Res1992; 13:113–119
36. Dailey JW, Yan QS, Adams-Curtis LE, Ryu JR, Ko KH, Mishra PK and Jobe PC. Neurochemical correlates of anti-epileptic drugs in the genetically epilepsy-prone rat (GEPR). Life Sci.1996; 58:259–266.
37. Peroutka SJ. 5-Hydroxytryptamine receptor subtypes: molecular, biochemical and physiological characterization. Trends in neurosciences, 1988; 11(11);496-500
38. Masand PS and Gupta S. Selective serotonin-reuptake inhibitors: an update. Harv Rev Psychiatry 1999; 7(2):69-84.
39. Bigler, E D. Neurophysiology, neuropharmacology and behavioral relationships of visual system evoked after-discharges: A review. *Neurosci Biobehav Rev 1977; 1*(2), 95–112.
40. Browning RA, Nelson DK. Variation in threshold and pattern of electroshock-induced seizures in rats depending on site of stimulation. Life science 1985; 37(23): 2205-2211.
41. Kasthuri S. A review: animal models used in the screening of antiepileptic drugs neuropsy. Int. Res J of pharmaceutical and Appld Sci. (IRJPAS), 2013; 3(3):18-23.
42. Jana Vasković. Neurotransmitters. Available at ken https://www.kenhub.com/en/library/anatomy/neurotransmitters(2022).Accessed 30/03/2023.
43. Chau PL. New insights into the molecular mechanisms of general anaesthetics. Br J Pharmacol 2010; 161(2):288-307
44. Löscher W, Rogawski MA. How theories evolved concerning the mechanism of action of barbiturates. Epilepsia2012; 53 Suppl 8:12-25.
45. Martone CH, Nagelhout J, Wolf SM. Methohexital: a practical review for outpatient dental anesthesia. Anesth Prog.1991; 38(6):195-199.