Progabide as Antiepileptic Drug for Epileptic Seizures

Undergraduate Project

An Undergraduate Project Submitted in Partial Fulfillment of the Requirements for the Degree of Bachelor in Medicine at University of Diyala/College of Medicine

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2023-2024

ABSTRACT

People of different racial backgrounds, genders, and ages can be affected by epilepsy, which is a heterogeneous condition. People who have epilepsy may also experience different types of seizures and epilepsy disorders. In addition to a variety of symptomatic indications include brain damage, stroke, infections, tumors, and developmental abnormalities, there are a wide range of underlying causes of epilepsy. The course of treatment for epileptics might differ significantly based on a number of clinical criteria. The primary goal of this research was to examine how well epilepsy patients responded to Progabide, an antiseizure drug. Since age and epileptic seizures are highly correlated, we also looked into how age can affect epileptic seizures.

A total of 59 participants were included in our data sample and were split into two groups: progabide (a group that took progabide medication for four days consecutively) and placebo. The Placebo group consisted of 28 participants, while the Progabide group contained 31. Each participant in both groups received treatment for four days throughout the specified period of time, which was included in the data. We also included each subject's age and daily seizure rate in our sample of data.

According to our research, the frequency of seizures decreased in patients on Progabide, however this decrease was not statistically significant. The findings align with multiple studies on the impact of Progabide on epileptic seizures carried out in both human and animal models. Our findings show that the age-related increase in seizure rate was observed in the Placebo group. Participants in Progabide who are under thirty years old had a similar outcome, but in those who are older than thirty, the effect is reversed, which may be related to how Progabide affects seizures. Thus; Progabide appears to be as effective as primary antiepileptic drug in treating patients with epilepsy.

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Chapter One

Introduction

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1. Introduction

Epilepsy is a common neurological disorder characterized by recurring seizures. Different types of epilepsy have different causes (Beghi E,2020). The brain or specific brain regions that are hyperactive and send too many messages are associated with epilepsy. This leads to epileptic fits, which are seizures. While seizures can occasionally just result in a few muscles twitching, they can also cause your entire body to spasm, or shake violently, leaving you unconscious (Stafstrom CE and Carmant L, 2015). You can develop epilepsy at any age. Some people experience their first seizure as early as childhood, while others do not experience one until they are much older (Stafstrom CE and Carmant L, 2015).

Both seizure prevention and preserving a high quality of life are made possible by medication. Regretfully, about 3 out of 10 people still experience regular seizures, so it's not always helpful. They find it more challenging to cope with their epilepsy because of this. In 2015, Stafstrom CE and Carmant L. With anti-epileptic medications (AEDs), two thirds of individuals with active epilepsy have satisfactory epilepsy control. Surgery is one of the other methods. In addition to improving health outcomes, optimal management can lessen other, frequently negative effects on social, educational, and occupational activities (National Institute for Health and Care Excellence, 2021). AEDs that have demonstrated clinical and financial efficacy must be found, as the prescription of more modern and costly AEDs is becoming commonplace. This is crucial given the likelihood of rising treatment costs in the years to come (National Institute for Health and Care Excellence, 2021).

Progabide (PGB) is the first antiepileptic molecule synthesized on a theoretical basis: the gamma-aminobutyric acid-(GABA)-ergic theory of epilepsy. It is a GABA-agonist which can cross the blood-brain barrier. Its pharmacological properties as an anticonvulsant are due to its specific activity as GABA receptor agonist (Loiseau P and Duche B, 2020). In order to treat epilepsy in both children and adults, specifically generalized tonic-clonic, myoclonic, partial, and Lennox-Gastaut syndrome seizures, progabide is approved for use in France as either a monotherapy or an adjuvant treatment (Musch, B *et al.*, 1987). This study aims to assess the effect of progabide on seizure rate in epilepsy patients and relate the rate to the age factor and investigate its effect as well.

1.1 Definitions of Epilepsy and Seizure

According to Fisher RS et al. (2005), a "clinical epileptic seizure" is characterized by aberrantly coordinated brain neuronal activity that results in momentary clinical indications or symptoms. According to Fisher RS et al. (2005), an epileptic seizure consists of the following components: aberrant increased synchrony, clinical symptoms, and the mode of start and termination.

Since a seizure is a transitory event, its beginning and end should be clearly marked. Because of the postictal phase, the clinical cessation of the seizure is typically less evident. A clinical seizure must exhibit at least one clinical sign, albeit they can vary greatly (Neligan A et al., 2012). According to Fisher RS et al. (2014), epilepsy is defined as a disease characterized by two or more unprovoked or reflex seizures that occur more than twenty-four hours apart, or as a single unprovoked or reflex seizure in a person who has a sixty percent chance of experiencing another seizure in the ensuing ten years.

In reference to the second criterion, the following two factors indicate that an individual has a 60% chance of experiencing another seizure during the next ten years:

- Brain imaging results with possible epileptogenic implications.
- Electroencephalogram (EEG) epileptiform activity

A single unprovoked seizure plus an aberrant brain imaging result (diffuse atrophy, arachnoid cyst, etc.) would not qualify as an epileptiform finding for the purposes of diagnosing epilepsy. (Fisher RS *et al.*, 2014).

1.2 Pathophysiology of Epilepsy

A portion of the brain or the entire brain may experience abnormal synchronized neuronal activity during epilepsy seizures. This can happen when brain networks are not properly created or are disrupted by an infectious, metabolic, or structural condition. Genetics, prenatal traumas, and abnormalities of cortical development are the most frequent causes of seizures in children (Aaberg KM et al., 2017). Brain tumors, traumatic brain injury, and encephalitis/meningitis are major causes of seizures in people without a hereditary predisposition to epilepsy (Bosak M et al., 2019). Epilepsy in older people is typically caused by brain tumors, head trauma, and primary neurodegenerative illnesses (Liu S et al., 2016; Cloyd J et al., 2006).

The etiology of epilepsy varies throughout age groups, leading to a bimodal prevalence of the condition: genetic/developmental reasons increase in childhood, while cumulative brain injury (such as trauma, tumors) peaks in old age (Tanaka A et al., 2013). The age-specific etiologies of epilepsy are shown in Figure (1-1). It is crucial to understand that in roughly 50% of instances, the cause of the seizures is unknown (Tanaka A et al., 2013).

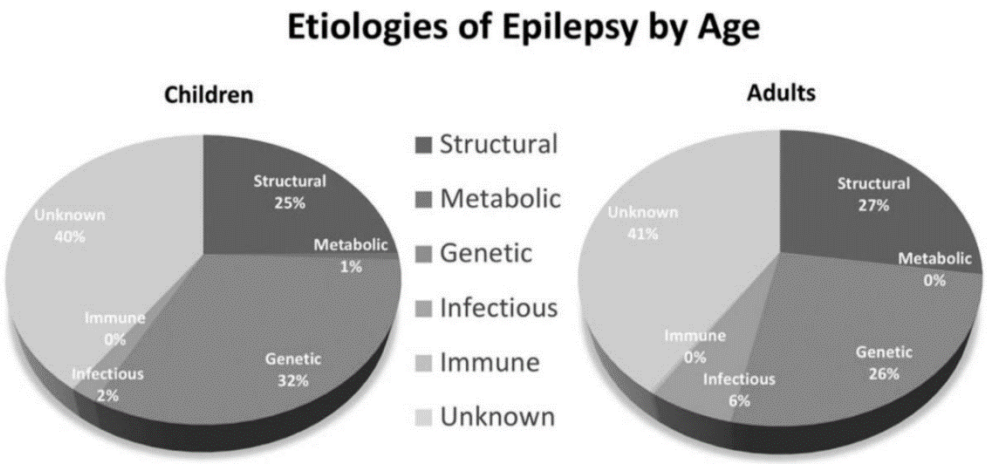

Figure 1.1: Etiology of epilepsy by age (Bosak M et al., 2019: Aaberg KM et al., 2017).

1.3 Epidemiology

In North America, the age-standardized incidence of epilepsy varies from 16 per 100,000 to 51 per 100,000 person-years. Depending on the reporting nation, the age-adjusted prevalence can vary from 2.2 of 1000 to 41 of 1000. Approximately two thirds of incidence epilepsies are classified as partial epilepsy. Lower socioeconomic groups have higher incidence (Banerjee PN et al., 2009). It is estimated that between 25% and 30% of seizures with a recent onset are either subsequent to or induced by another cause (Banerjee PN et al., 2009). The incidence of epilepsy is higher in younger and older age groups and rises gradually after the age of fifty. Cerebrovascular disease is the most common cause of epilepsy and seizures in older adults (Sen A et al., 2020).

1.4 Symptoms

There are big differences in epileptic seizures between people. Some simply affect one arm or one leg, while others affect the entire body. Some merely last a few seconds or even go undetected. People can experience three different states of consciousness: completely conscious, briefly mentally absent, and unconscious.

Seizures with epilepsy normally end quickly. Seizures lasting more than five minutes are called "status epilepticus." This is a medical emergency that needs to be treated with medication right away. Individuals may also experience many seizures in a brief period of time. The two primary types of epileptic seizures are as follows:

- ✓ Generalized seizures
- ✓ Partial (focal) seizures

1.4.1 Generalized Seizures

The entire brain is affected by generalized seizures. They aren't always more severe than partial seizures, which only impact a portion of the brain. However, generalized seizures are more likely to cause complete unconsciousness and convulsions throughout the body. Different kinds of generalized seizures exist, including:

1- Tonic seizures: The majority of the time, this type of seizure passes very rapidly and doesn't always impair consciousness.
2- Atonic seizures ("drop attacks"): It's also possible for you to faint momentarily and fall.
3- Clonic seizures: Usually, this is followed by unconsciousness.
4- Myoclonic seizures: Usually, this has no effect on your level of consciousness.
5- Tonic-clonic seizures (sometimes called "grand mal seizures"): You lose consciousness as your entire body twitches and convulses.
6- Absence seizures (sometimes called "petit mal seizures"): People who experience this moderate kind of seizure appear to "zone out" for a brief period of time, losing consciousness unexpectedly.

1.4.2 Partial (Focal) Seizure

Only one area of the brain experiences partial seizures. Depending on what that area of the brain performs, the symptoms could be anything from odd sensations (sensory

disturbances) to twitches in the arm (motor disturbances) to changes in eyesight (visual disturbances). Partial seizures can cause odd sensations, loss of consciousness, and altered hearing, vision, or smell. They might also experience anxiety, vertigo, or hallucinations. We call this an aura. Some people stroll around aimlessly, smack their lips, make faces, stammer, or mess with objects. Convulsions or twitches may accompany partial seizures. Partial seizures can occasionally impair consciousness or focus.

1.5 Treatment of Epilepsy

Finding an AED regimen that is both totally effective and causes no side effects for the patient is the aim of the many AEDs that have been on the market for a long time. The cost, teratogenicity, and drug-drug interactions of medications differ. Narrow-spectrum and broad-spectrum antiepileptic medications are separated (Chaves J and Sander JW, 2005).

Only a few types of seizures can be treated with narrow-spectrum AEDs; they may not be useful at all or perhaps make other seizures worse. Carbamazepine, oxcarbazepine, gabapentin, pregabalin, tiagabine, and eslicarbazepine are examples of AEDs with a narrow range. Myoclonic and absence seizures may worsen as a result of these AEDs (Chaves J and Sander JW, 2005).

For a variety of seizures, including focal, absence, generalized tonic-clonic, and myoclonic, broad-spectrum AEDs have some efficacy (Chaves J and Sander JW, 2005). Compared to previous medications, the more recent AEDs typically have less side effects. Fatigue, gastrointestinal side effects, mood swings, and cognitive side effects are possible adverse effects shared by all AEDs. According to Carbone LD et al. (2010), older generation AEDs are linked to a higher incidence of fractures

because of osteopenia and have more adverse effects. Anyone who has taken one of the following medications for five years or more is advised to get a bone density screening: phenytoin, phenobarbital, primidone, valproate, or carbamazepine (Harden CL, 2003; Andress DL et al., 2002).

1.5.1 Progabide

Gamma-aminobutyric acid has an analog and prodrug in the form of progabide. It is frequently applied to epilepsy treatment. It functions as an agonist on the GABAA and GABAB receptors. Progabide has been studied in clinical trials for anxiety disorders, schizophrenia, Parkinson's disease, and clinical depression; however, it is unclear how effective of a treatment progabide is for these ailments (Martinez-Lage et al., 1984).

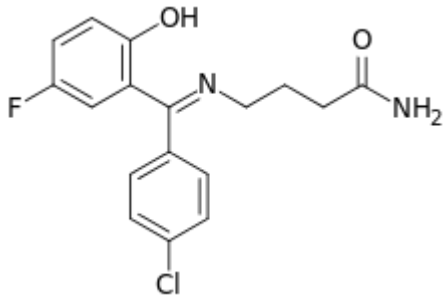

Figure 1.2: Structure of the Progabide

1.5.1.1 Mechanism of Action of Progabide

Progabide attaches itself to GABAA and GABAB receptors found on primary afferent fiber terminals. higher affinity of the GABA receptor for the amino acid, higher flux of chloride ions across the terminal membrane, and greater presynaptic inhibition are the outcomes of binding to GABAA. GABAB receptor activation

reduces the evoked release of excitatory amino acids and perhaps other transmitters by delaying the entrance of calcium ions into the terminals (Loiseau P and Duche B, 2020).

1.5.1.2 Side Effect of Progabide

The most common side effect of progabide is: (Stroup TS and Gray N, 2018)

1- Drowsiness
2- Dizziness
3- Headache
4- Nausea
5- Vomiting
6- Diarrhea

1.6 Progabide as an add-on drug for Epilepsy Refractory to High Dose Antiepileptic Drug Therapy

In a double-blind, cross-over add-on trial, 11 patients who were unable to control their intractable complex partial seizures with high doses of carbamazepine, phenobarbital, phenytoin, or primidone were given an average daily dose of 2100 mg progabide or placebo for three months each. In one patient each, there was a decrease or rise in seizure frequency of greater than 50%. Two patients experienced mild, transitory sedative side effects. The concurrent antiepileptic medications' plasma concentrations did not alter (Schmidt, D, 1984).

When used as an adjuvant therapy for partial epilepsy that has not responded to prior high-dose therapy, progabide seems to be just as effective as a primary antiepileptic medication. Despite its few adverse effects, progabide does not appear to be the medication that is desperately needed for routine therapy failures (Schmidt, D, 1984).

1.7 The Addition of Progabide to Standard Anticonvulsants Improves Epilepsy Control but Liver Function Should Be Monitored

The addition of progabide to standard anticonvulsant therapy in patients with refractory epilepsy beneficially affects seizure control. In a double-blind. crossover study. 51 patients received their standard anticonvulsant therapy (comprising I or 2 agents). plus progabide 30-40 mg/day or placebo for 8 weeks each.

Both patients and clinicians preferred progabide to placebo. Six patients were free from seizures during progabide therapy compared with 2 patients during placebo therapy. Seizure frequency was reduced by ~ 50% in 18 patients during progabide therapy and in 8 patients during placebo administration. Increases in phenytoin and carbamazepine concentrations were seen in 3 and I patient(s). respectively. Two patients were withdrawn from the study because of elevated aminotransferase levels which occurred during progabide therapy (clinical hepatitis developed in 1 of these patients): 1 further patient was withdrawn after an acute psychotic episode. 24 patients entered an open study of progabide therapy: 17 completed 9 months' follow-up with beneficial results. The authors concluded that progabide "is useful in patients not responding to available AEDs [anticonvulsant drugs], provided that monitoring of liver function tests is assured" (Feldman S, 1991).

1.8 Effects of Progabide on Bicuculline-Induced Epileptic Seizures in Developing Rats

Progabide is a direct γ-aminobutyric acid (GABA) receptor agonist. Its effects on bicuculline-induced seizures have been investigated in developing rats (7–28 days) to determine the relationship between the drug's antiepileptic efficacy and the degree of GABAergic system functional maturation. Rats that received either a single injection (treatment) or three daily administrations (pretreatment) of progabide were used to assess the incidence, latency of appearance, behavioral features, and

evolution of epileptic manifestations toward status epilepticus, as well as the percentage of recovery from status epilepticus. The outcomes have been contrasted with those of an animal control group that received an injection of solely bicuculline. The medication appears to be largely unsuccessful in preventing bicuculline seizures and their effects in rats aged 7–14 days. This is likely due to the GABAergic system's significant immaturity at birth and in the early stages of life. At this age, repeated progabide injections produce a more notable protective anticonvulsant effect than a single injection, especially when utilizing greater dosages of the drug. Treatment considerably lowers the mortality from status epilepticus in rats aged 15–28 days, but it has no discernible effect on the frequency of seizures, the latency of their onset, or the progression of the seizures toward status epilepticus. Regardless of the dosage of progabide administered, pretreatment is more efficacious than treatment for bicuculline seizures in aged rats, just as it is in younger animals. Therefore, according to biochemical data on the GABAergic system ontogenesis, at this age the anticonvulsant characteristics of progabide become more impressive than in the previous age, likely due to a higher level of development of the GABAergic system. (Mecarelli O *et al.*, 1988).

1.9 A comparative Study of Progabide, Valproate, and Placebo as Add-on Therapy in Patients with Refractory Epilepsy

Progabide, valproate, and placebo were compared in a three-way single blind cross-over trial as supplemental therapy for 64 patients with partial and generalized seizures who were not responding to previous treatments. Because progabide was associated with an incidence of increased liver enzymes, the trial was not completed. Progabide was found to be less effective than valproate in treating all forms of seizures, especially tonic-clonic seizures. When it came to partial and tonic-clonic seizures, valproate outperformed a placebo. In every case, there was no discernible

difference between placebo and progabide. Furthermore, progabide was linked to an interaction with phenytoin that in certain cases produced intoxication symptoms, and it elevated liver enzymes in one case that was symptomatic (Crawford P and Chadwick D, 1986).

Chapter Two

Methods and Materials

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2.1 Subjects and Data Collection

There is currently no model that can cover all seizure phenotypes and precisely match genuine seizure characteristics. Given the diversity of seizure features, model selection may be depending on specific needs in practice. Thus, epilepsy datasets are particularly difficult since they are generated in a variety of situations using different terminologies. To address this issue and assist academics conducting epilepsy research, various internet sites made large datasets available for free. Because there are no facilities in Diyala that can provide us with epilepsy data, we used data from Kaggle website. Our data sample included 59 subjects who were divided into two groups: placebo (a group that receives what appears to be a treatment, but is actually neutral and does not contain any active treatment and progabide (a group in which subjects took progabide medicine for four days in a row). The Progabide group had 31 subjects, while the Placebo group included 28. The data included the period of the treatment of each individual in both groups (four days of treatment for each subject). The daily seizure rate and the age of each subject were provided in our sample of data as well.

2.2 Statistical Analysis

Seizure rate of Placebo and Progabide groups was statistically evaluated using Wilcoxon signed-rank test. Wilcoxon rank-sum test (Mann–Whitney test) was used to assess the effect of age on seizure rate. Statistical significance was defined as a *p*-value of less than 0.05.

In addition, the seizure rates of the data pooled from all participants in the two groups (Placebo and Progabide) were presented as empirical cumulative distribution data (ECDF) and compared using the Kolmogorov-Smirnov test.

Chapter Three

Results and Discussion

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3.1 Data Distribution based on the Treatment and Age Factors

Based on the treatment that subject in each group received, the data was classified into two groups: Placebo and Progabide groups. The Placebo group had 28 participants while Progabide group had 31 participants. Figure (3.1.a) shows the data distribution of each group, placebo individuals represented 47% and Progabide the remaining 53%. Data were collected from each participant for four days which makes it fair and reliable in comparing between the two groups to investigate the effect of the treatment on epileptic seizures. In each of the two categories, the data was then subdivided into subgroups based on the age characteristics. The distribution of data in each group is depicted in figure (3.1.b). Figure (3.2) shows the data distribution of each individual in each group.

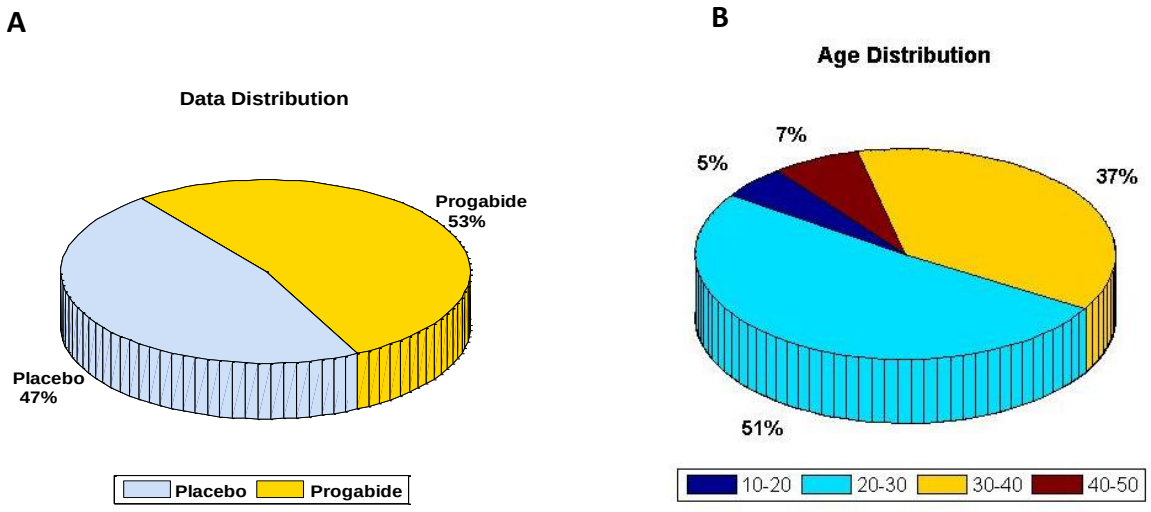

Figure 3.1: Data Distribution based on the treatment and Age Factors.

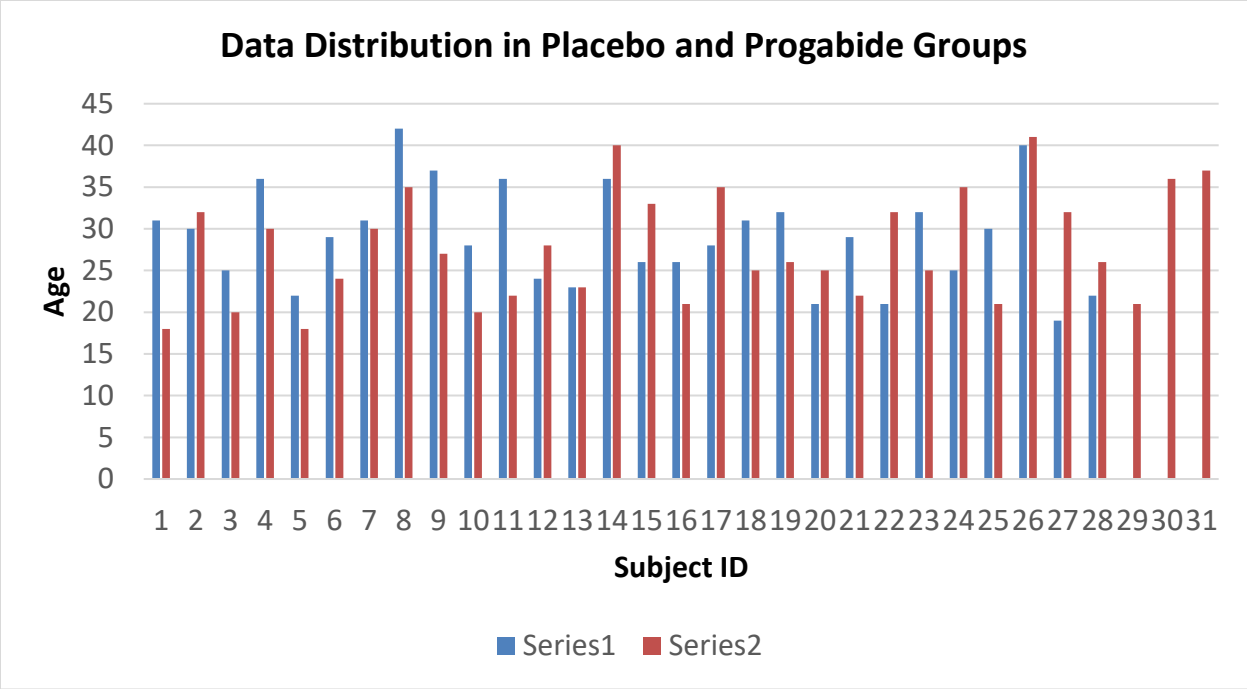

Figure 3.2: Data Distribution based on age in each group. Series 1 refers to the Placebo and series 2 to the Progabide group.

3.2 Effect of Progabide Treatment on Seizure Rate

The difference in the epileptic seizure rate between the Placebo and Progabide groups was statistically evaluated using the signed rank Wilcoxon test. Our results revealed that there is a reduction in the seizure rate in subjects who underwent to the Progabide treatment (see figure 3.3.a) but that reduction did not reach the level of significance (P-value= 0.1947). The seizure rates of all individuals in each group were plotted as am ecdf and statistically evaluated. Again, there was a clear decrease in the rate of seizures in Progabide individuals compared to those of Placebo group (figure 3.3.b). Our results are consistent with the results of M. Dam., et.al , in which they found that there is no significant difference was established between the number of partial seizures during treatment with progabide and placebo. They approved that a trend was observed for lower seizure frequency of secondary generalized seizures during treatment with progabide. Only mild and transient side effects were observed.

There was no difference between the side effects of progabide and placebo. Looking at the effect of the Progabide on seizure frequency on each day of the treatment, it was obvious there is a reduction in the number of seizures on the first three days, there was no clear effect on the four day as shown in figure 3.4.

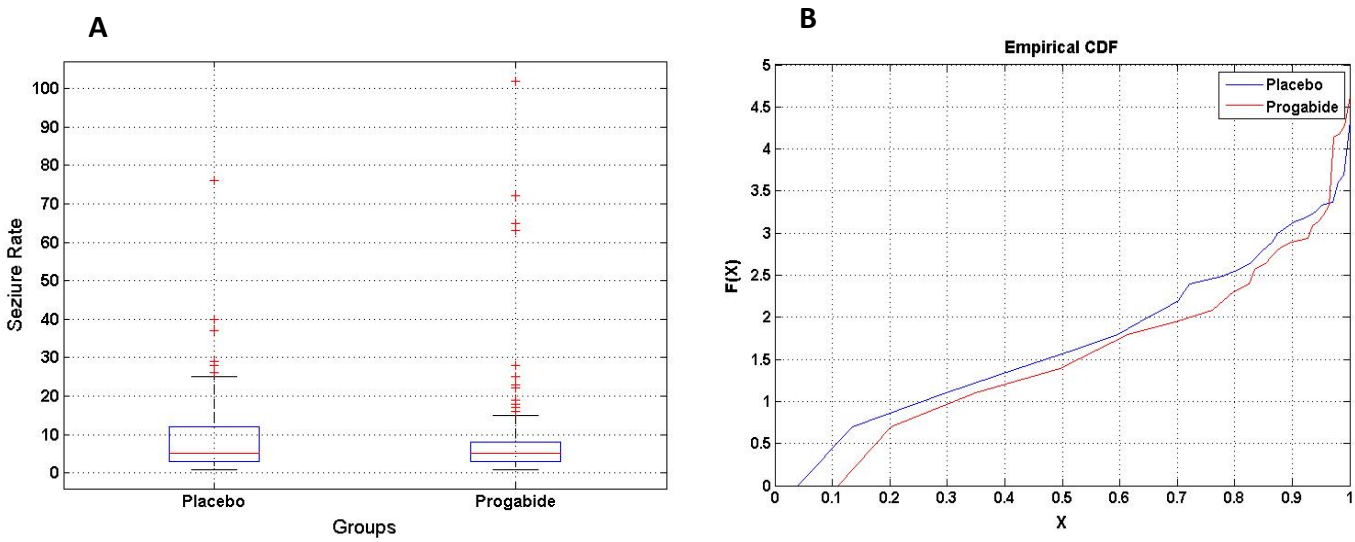

Figure 3.3: Effect of the Progabide on Seizure Rate

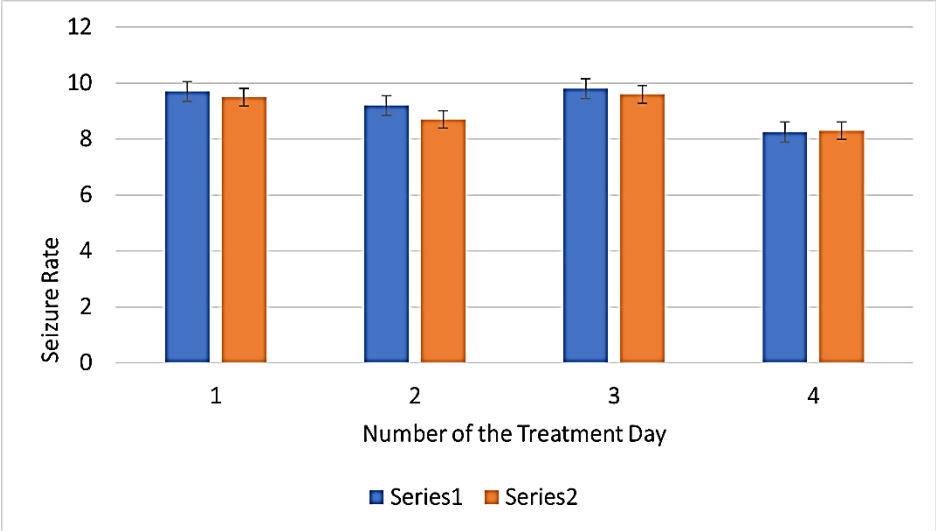

Figure 3.4: Effect of Progabide on Seizure Rate on Daily Basis

3.3 Effect of Age on Epileptic Seizures

The ages of the participants range from 10 to 45, as shown in figure (3.2). As a result, we divided each of the Placebo and Progabide groups into four smaller groups according to age. The following age ranges made up the four subcategories: 10–20, 20–30, 30–40, and 40–50 years old. Using the rank sum test, the impact of age in each group was statistically assessed. The effect of age on seizure frequency in each of the subgroups is depicted in Figure 3.5. There were discernible variations in the seizure rate with age, even though there was no significant influence in the Placebo group (p-value > 0.05). You can observe that the Placebo group (series 1; blue in figure 3.5) has a higher seizure rate as they get older. Our findings are in agreement with the literature's documentation of the impact of aging on epilepsy, as seizures are recognized to be frequent neurologic occurrences in the elderly that may manifest with subtle differences. Interestingly, when examining the impact of age on seizure rate in the Progabide group (series2, orange in figure 3.5), it appears that there is a notable rise in the second group's seizure rate (20–30) when compared to the first group's (10–20) years old, followed by a decline in the third and fourth groups' seizure rates. This decrease might indicate that Progabide is a useful antiepileptic medication for people with epilepsy who are older than thirty. Therefore, it is possible to predict that, even if the long-term impact of seizure activity on the neurodegenerative illness is unknown, treating epilepsy is advantageous to the patient. When acute seizures start, it's important to start anticonvulsant and neuroprotective therapy as soon as possible to prevent or lessen the severity of acute seizures-related cognitive impairment in the elderly.

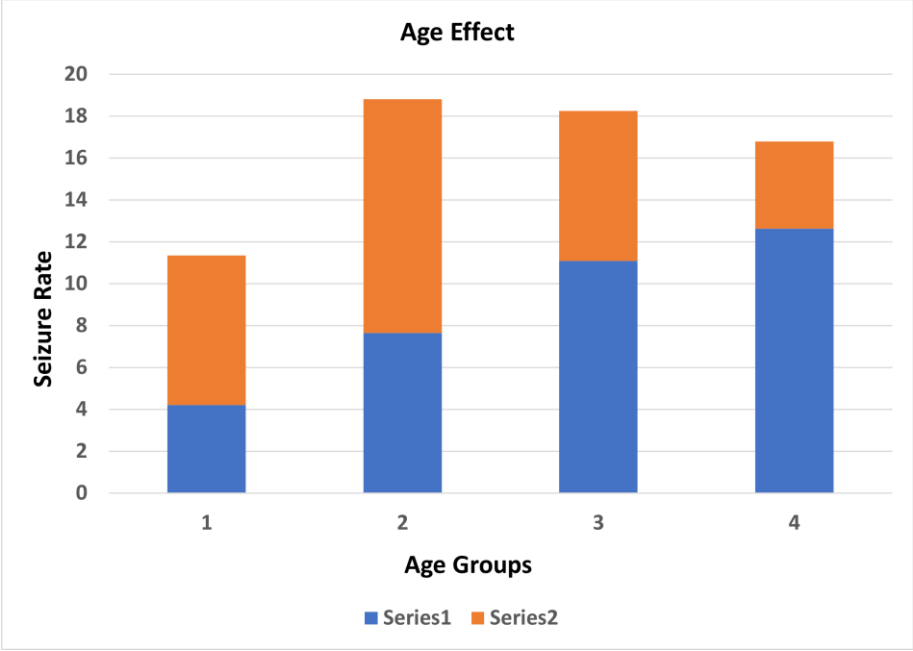

Figure 3.5: Effect of Age on Seizure Rate. Series 1: indicate the Placebo group and Series 2: indicates the Progabide group.

Chapter Four

Conclusions and Future Directions

Chapter Four
Conclusions and Future Directions

Our results have demonstrated qualitative changes of the action of progabide during in epilepsy patients. Our findings showed that patients receiving Progabide medication experienced a decrease in seizure frequency, however this decrease did not approach statistical significance. The results are consistent with several research that were conducted in humans and animal models of epilepsy about the effect of Progabide on epileptic seizures.

Age plays a significant role in the clinical and electroencephalographic aspects of seizures, and the causes and effects of epilepsy are known to be age-related. Our research indicates that the Placebo group's seizure rate increased with age. The similar result was seen in the Progabide participants who are with age range below thirty but the effect is reversed in subjects over thirty years old which could be explained by the effect of the Progabide on seizure attacks.

Taking into account the extent and constraints of this research as well as the goal of future therapeutic usefulness, the following necessary future directions can be suggested: A larger sample size would increase the confidence in Progabide's efficacy as a medication for treating patients with epileptic seizures, gender factor, patients at high risk for SUDEP would also help us better understand the relationship and underlying mechanisms between epilepsy and SUDEP, and identifying the type of epilepsy will add further value to this research.

References

1- Stafstrom CE, Carmant L. Seizures and epilepsy: an overview for neuroscientists. Cold Spring Harbor perspectives in medicine. 2015 Jun;5(6).

2- Beghi E. The epidemiology of epilepsy. Neuroepidemiology. 2020 Dec 18;54(2):185-91.

3- NICE Clinical Guidelines, No. 137, Epilepsies: diagnosis and management, London: National Institute for Health and Care Excellence (NICE); 2021 May 12.

4- Loiseau P, Duche B. Progabide. InThe Medical Treatment of Epilepsy 2020 Sep 10 (pp. 393-398). CRC Press.

5- Musch, B., Cambier, J., Loiseau, P., Fournier, V., Beaussart, M., Benoit, C., … Roger, J. (1987). Long-Term Treatment of Epilepsy: Open Multicenter Trial with Progabide in Epileptic Patients. European Neurology, 26(2), 113–119. doi:10.1159/000116320

6- Aaberg KM, Surén P, Søraas CL, et al. Seizures, syndromes, and etiologies in childhood epilepsy: The International League Against Epilepsy 1981, 1989, and 2017 classifications used in a population-based cohort. Epilepsia 2017;58(11):1880–1891

7- Bosak M, Słowik A, Kacorzyk R, Turaj W. Implementation of the new ILAE classification of epilepsies into clinical practice - a cohort study. Epilepsy Behav 2019;96:28–32

8- Liu S, Yu W, Lü Y. The causes of new-onset epilepsy and seizures in the elderly. Neuropsychiatr Dis Treat 2016;12:1425–1434

9- Cloyd J, Hauser W, Towne A, et al. Epidemiological and medical aspects of epilepsy in the elderly. Epilepsy Res 2006;68(Suppl 1): S39–S48

10- Tanaka A, Akamatsu N, Shouzaki T, et al. Clinical characteristics and treatment responses in new-onset epilepsy in the elderly. Seizure 2013;22(09):772–775

11- Banerjee PN, Filippi D, Allen Hauser W. The descriptive epidemiology of epilepsy-a review. Epilepsy Res. 2009 Jul;85(1):31-45.

12- Sen A, Jette N, Husain M, Sander JW. Epilepsy in older people. Lancet. 2020 Feb 29;395(10225):735-748.

13- Neligan A, Hauser WA, Sander JW. Chapter 6: The epidemiology of the epilepsies. In: Stefan H, Theodore WH, eds. Handbook of Clinical Neurology, Vol. 107. Amsterdam: Elsevier; 2012: 113–133

14- Fisher RS, van Emde Boas W, Blume W, et al. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). Epilepsia 2005;46(04):470–472

15- Fisher RS, Acevedo C, Arzimanoglou A, et al. ILAE official report: a practical clinical definition of epilepsy. Epilepsia 2014;55(04): 475–482

16- Chaves J, Sander JW. Seizure aggravation in idiopathic generalized epilepsies. Epilepsia 2005;46(Suppl 9):133–9.

17- Carbone LD, Johnson KC, Robbins J, et al. Antiepileptic drug use, falls, fractures, and BMD in postmenopausal women: findings from the women's health initiative (WHI). J Bone Miner Res 2010;25:873– 81.

18- Andress DL, Ozuna J, Tirschwell D, et al. Antiepileptic drug-induced bone loss in young male patients who have seizures. Arch Neurol 2002;59:781–6.
19- Harden CL. Menopause and bone density issues for women with epilepsy. Neurology 2003;61:S16–22
20- Martinez-Lage, Jose & Bossi, Laura & Morales, G & Vila, E. & Orofiamma, B & Viteri, César. (1984). Progabide Treatment in Severe Epilepsy: A Double-Blind Cross-over Trial Versus Placebo. Epilepsia. 25. 586-93. 10.1111/j.1528-1157.1984.tb03466.x.
21- Loiseau P, Duche B. Progabide. InThe Medical Treatment of Epilepsy 2020 Sep 10 (pp. 393-398). CRC Press.
22- Stroup TS, Gray N. Management of common adverse effects of antipsychotic medications. World Psychiatry. 2018 Oct;17(3):341-56.
23- Schmidt, D. (1984). *Progabide as an add-on drug for epilepsy refractory to high dose antiepileptic drug therapy. Neuroscience Letters, 47(3), 357–360.* doi:10.1016/0304-3940(84)90539-1
24- Feldman S. The addition of progabide to standard anticonvulsants improves epilepsy control, *Inpharma Wkly.* **780**, 9 (1991).
25- Mecarelli O, De Feo MR, Rina MF, Ricci GF. Effects of progabide on bicuculline-induced epileptic seizures in developing rats. Clinical neuropharmacology. 1988 Oct 1;11(5):443-53.
26- Crawford P, Chadwick D. A comparative study of progabide, valproate, and placebo as add-on therapy in patients with refractory epilepsy. Journal of Neurology, Neurosurgery, and Psychiatry. 1986 Nov;49(11):1251.
27- Progabide: A Controlled Trial in Partial Epilepsy
28- M. Dam, L. Gram, A. Philbert, B. S. Hansen, B. Blatt Lyon, M. Christensen, H. R. Angelo. First published: April 1983 https://doi.org/10.1111/j.1528-1157.1983.tb04873.x