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Research article

COMPARATIVE ANTI-CONVULSANT ACTIVITY FOR EVALUATION OF PHARMACODYNAMIC DRUG INTERACTION OF NEW ANTI EPILEPTICS LAMOTRIGINE WITH PHENYTOIN (CYP3A4 ENZYME INDUCER) AND SOD VALPROATE (ENZYME INHIBITOR) BY MAXIMAL ELECTRO SHOCK (MES) INDUCED SEIZURES MODEL USING ELECTROCONVULSIOMETER IN SPRAGUE DAWLEY RATS

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ABSTRACT

The present study attempts to investigate the anticonvulsant activity and pharmacodynamic interactions of Lamotrigine with Phenytoin and Sodium valproate in maximal electroshock (MES) induced seizures on males Sprague Dawley (SD) rats. Seizures were induced in SD rats (100-200 g) by delivering maximal electro shock of 150 mA for 0.2 sec by means of a convulsiometer through a pair of ear clip electrodes. The test compounds [Phenytoin (25mg/kg), Sodium valproate (300mg/kg)] and Lamotrigine (18mg/kg) were administered by oral route one week before and an hour before the MES test respectively. The animals were observed closely for 2 mins. The percentage of inhibition of seizure by measuring the time taken behavioral relative to control was recorded and calculated. Phenytoin (100 mg/kg) was used as a standard drug. The data was analysed by using one way ANOVA. As per the observation, the Lamotrigine along with the sodium valproate shows more significant variation than that of the Lamotrigine with the Phenytoin when compared with that of the Lamotrigine alone. All the three groups (groups-1,2,3) of drugs shows more variation compared with control group (group-1). The increased levels of the Lamotrigine in case of Group-3 (enzyme inhibitor) may increase the risk of adverse effects, whereas decreased levels of Lamotrigine in case of Group-2 (enzyme inducer) may automatically decrease the antiepileptic activity of Lamotrigine. So, it is fore most important to have Therapeutical Drug Monitoring (TDM) of Lamotrigine during its concomitant use throughout the therapy.

Key Words:- Epilepsy, Lamotrigine, MES (Maximum electro shock), Drug interactions, TDM.

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INTRODUCTION

History Of Epilepsy

The term epilepsy was derived from the ancient Greek word 'epilambanein' which means 'to seize or to take hold of' or attack. Epilepsy therefore means "a condition of getting over, seized or attacked." Later, epilepsy is defined as a common chronic neurological disorder characterized by recurrent unprovoked seizures (or convulsions) (Commission, 1989; Blume*et al*, 2001). Seizures are transient signs and/or symptoms of abnormal, excessive or synchronous neuronal activity in the cortical area of the brain (Fisher *et al*, 2005). A seizure is a symptom and not a disease and may or may not evoke clonic jerking of the body parts controlled by the cortex with evident muscular convulsive episodes. Seizures can be non-epileptic when evoked in a normal brain by treatments such as electroshock or chemical convulsant or epileptic when occurring without evident provocation (McNamara, 2006). An individual can experience a seizure under certain conditions such as marked hypoxia, severe hypoglycemia, very high fever 4 (febrile convulsion), or if giving an electrical shock to the head during electroconvulsive therapy. However, epileptic seizures are the behavioral manifestation of abnormal brain neuronal activity. It is characterized by the recurrent, usually transient, abrupt episodes of disturbed brain function with or without loss of consciousness, altered psychic function and convulsive movements (Davis *et al*, 2005).

EPIDEMOLOGY

Epilepsy is one of the most common chronic neurological disorders in the world. According to the WHO report, it affects about 50 million people worldwide with almost 90% of these people found in the developing countries (WHO, 2001; Hirtz*et al*, 2007). Genetic, congenital and developmental conditions are mostly associated with epilepsy among young patients while tumors are more likely over the age of 40. Also head trauma and central nervous system infections may occur at any age. The prevalence of active epilepsy is roughly in the range 5-10 per 1000 people while the incidence rate is 40-70 and 100-190 per 100,000 people in industrialized and developing countries respectively (Sander, 2003). In sub-Saharan Africa (SSA), there is a high prevalence of this disorder with Cameroon and Tanzania leading with prevalence rates of 58 and 35 per 1000 people respectively whereas Nigeria has 5.3 per 1000 (Osuntokun*et al*, 1987; Diop*et al*., 2003; Preux and Druet-Cabanac, 2005). Certain diseases also seem to occur in higher than expected rates in people with epilepsy. These include depression and anxiety disorders, migraine, infertility, low sexual libido, autism and attentiondeficit / hyperactivity disorder (ADHD). ADHD affects three to five times more children with epilepsy than children in the general population (Plioplys*et al*, 2007; Levisohn, 2007).

ANTIEPILEPTIC DRUGS

Antiepileptic drugs (AED's) are used in the treatment of epilepsy which has been a major disease since several decades. Earlier epilepsy has been characterized by the occurrence of repeated seizures by firing of the neurons without an appropriate definition. Epilepsy has a history nearly from 2000 B.C to till today. For the first time the term epilepsy was reported in the book "THE SACRED DISEASES" by Hippocrates. The word epilepsy was derived from a Greek work "EPILEPSIA" which means "to take hold" or "to seize". Prior to all the drugs used as anti-epileptics, a compound known as BROMIDE used as first effective antiepileptic drug by Sir Charles Locock in year 1857.This bromide became widely used drug in Europe and North-America during second half of last century. The first hospital for 'paralyzed and epileptic' was established in 1857 at London.

The main drugs used for the treatment of epilepsy during the first half of this century were phenobarbitone (1912), phenytoin (1939). Since 1960's the process of drug discovery for epilepsy were accelerated based on the electrochemical activities of the brain like the excitatory and inhibitory neurotransmitters. Now-a-days several new drugs got invented into the market for the treatment of epilepsy. By the newly invented drugs the epilepsy can be controlled in approximately 75% of newly diagnosed children and adult.

At present, preclinical animal studies are indispensable in exploring the efficacy and safety of an investigational AED before its introduction in human volunteers. Although modern cellular neurophysiological and biochemical approaches have made it possible to identify molecular targets of AEDs, *in vitro* testing is not likely to replace screening in animal models: on the one hand, *in vitro* systems cannot model the specific pharmacodynamic actions required for seizure protection since they do not assess the multidimensional parameter space, which includes not only the target molecules but also critical biomolecules that could cause side effects or interfere with the desired activity; on the other hand, *in vitro* testing does not assess bioavailability, brain accessibility and local delivery to the target. Therefore, only animal test systems can select compounds that are inherently anticonvulsant and are able to access the relevant brain targets. If the purpose of the research is not to study the epileptic phenomenon itself but to screen new AEDs, the animal models fall into two main categories: models of acute seizures (nonepileptic animals induced to have a seizure by an electrical or chemical stimulus) and models of chronic epilepsy (animals induced to have enhanced seizure susceptibility

or spontaneous seizures. For practical reasons, experimental research on new AEDs has mostly been carried out on normal mice and rats in which seizures were induced by chemical or electrical means. Indeed, with respect to screening purposes, electrically or chemically induced seizures have advantages over most genetic models since seizure-susceptible animal species may lead to an exaggeration of the anticonvulsant potency of a new drug.

Over the years, the maximal electroshock seizure (MES) model has remained one of the gold standards in early stages of testing. In our opinion, despite the continuous search for new models closer to the human epilepsy phenomenon, the MES model will persist as the most useful tool at least at the anticonvulsant compound identification stage. Hence, we intend to describe in a single paper all the useful yet dispersed information on performing anticonvulsant screening by MES tests, drawing particular attention to experimental procedures and factors affecting the accuracy of experimental data.

AIM AND OBJECTIVE:

AIM:

To study the comparative anti- convulsant activity for evaluation of pharmacodynamic drug interactions of new anti- epileptics.

OBJECTIVE:

To determine the anti- convulsant activity for evaluation of pharmacodynamic drug interactions of new anti- epileptics Lamotrigine with phenytoin (CYP 3A4 enzyme inducer) and Sodium valproate (enzyme inhibitor) by using Maximal Electro Shock (MES) induced seizures model using Electroconvulsiometer in Sprague dawley rats.

1. To check the pharmacodynamics drug interaction of antiepileptic drugs.
2. To observe the activity of lamotrigine on rats by MES.
3. To find the effect of phenytoin and sodium valproate on antiepileptic activity of Lamotrigine.

METHODS & MATERIALS:

Duration of the project: 2 months
Date of initiation (Proposed) : 01/11/2018
Date of completion (Proposed) : 02/01/2019

PHASE-I

- Animal procurement & quarantine of Sprague Dawley Rats.
- Induction of convulsions using Electroconvulsive meter in SpargueDawley Rats.

PHASE – II

- Grouping the quarantined animals as per the treatment.
- One-week prior treatment of animals for successful enzyme induction & enzyme inhibition once daily.
- Giving the test compound 60min prior to MES on the day of experimentation.

PHASE-III

- Interpretation of results

Test samples:

Drugs	Doses (mg/kg)
Phenytoin	25 (IP)
Sodium valproate	300 (IP)
Lamotrigine	18 (IP)

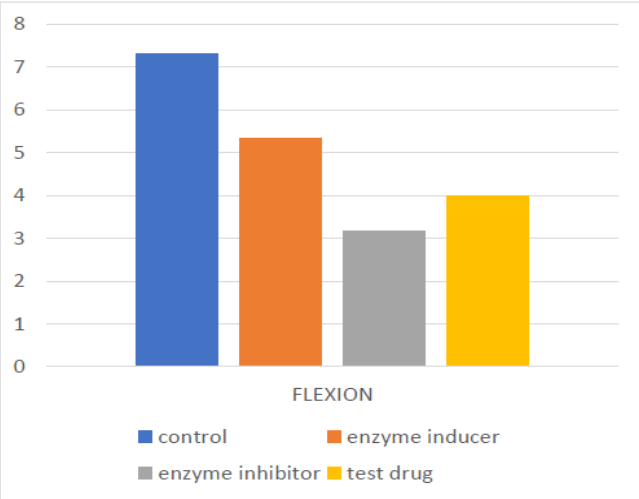
Table 1: Duration of different stages of seizures

Characteristics / Groups	Mean ± standard deviation (in seconds)			
	Flexion	Extension	Clonus	Stupor
Group-1	7.298±0.97	10.05±2.23	59.535±12.89	144.66±17.45
Group-2	5.328±0.73*	3.938±1.06*	40.198±8.601*	113.83±25.49*
Group-3	3.158±1.01*	5.325±0.89*	25.81±8.55*	93.33±41.18*
Group-4	3.988±0.59	9.03±1.5	32.4±5.95	115.16±30.109

*$P < 0.05$, hence it is significant.

Figure 1: Flexion: Joints are pulled closer

Figure 2: Extension: Angle of hind limbs exceeds 90^0



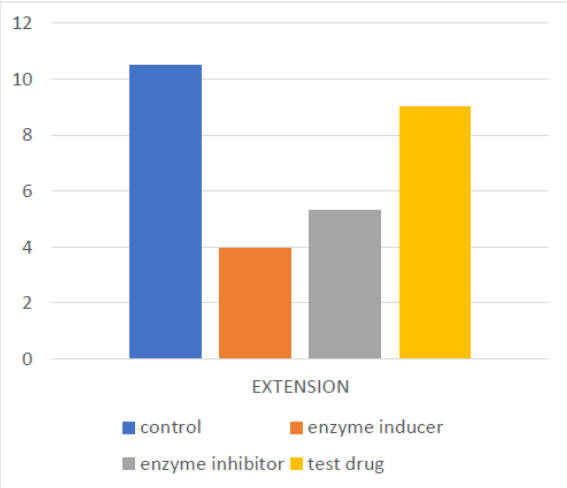
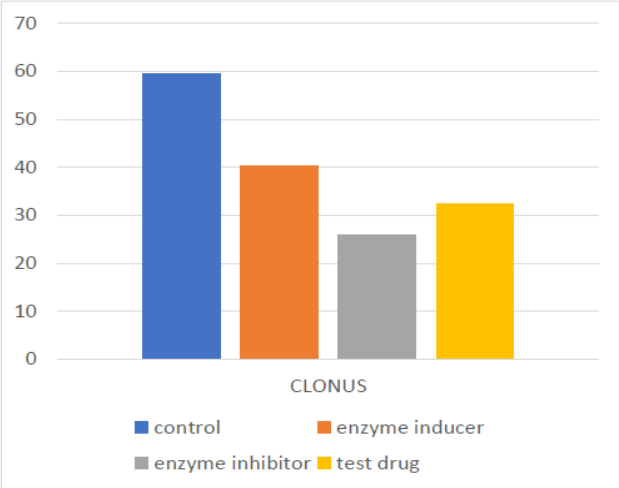


Figure 3: Clonus: Rhythmic contraction of limbs

Figure 4: Stupor: A state of near unconsciousness or insensibility



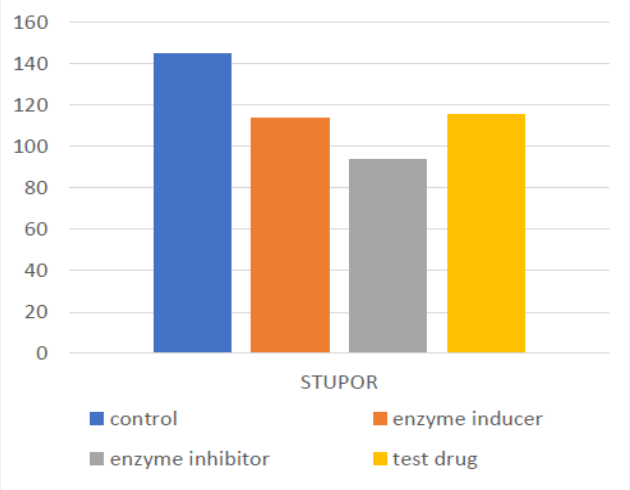
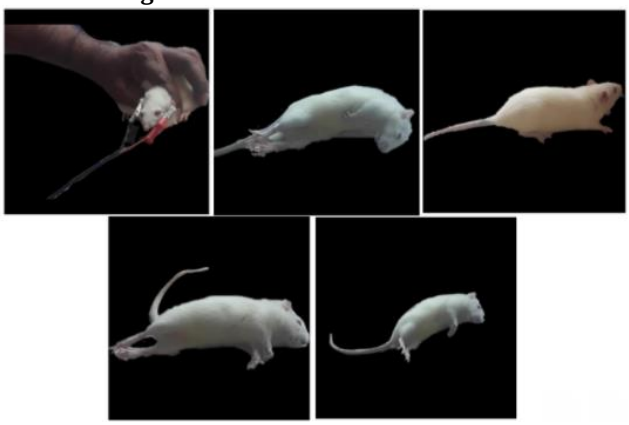


Figure 5: STAGES OF EPILEPSY



DISCUSSION:

This study was performed in healthy rodents, which is a major limitation of this study. It would have been of more translational value in doing this study in true epilepsy models for instance, animal mutants or transgenic animals with spontaneously recurrent seizures, which are more closely related to seizure models like MES (maximal electroshock seizure).

In the present study we investigated the effects of commonly used first line AEDs which included newer antiepileptic like Lamotrigine, in comparison with the control group and conventional antiepileptics sodium valproate and Phenytoin in SD rats.

The MES is probably the best-validated method for assessment of anti-epileptic drugs in generalized tonic-clonic seizures. MES causes several changes at the cellular level, which can disrupt the signal transduction in the neurons. One of the most important mechanism by which it causes cellular damage is the facilitation of Ca 2+ entry into the cell in a large amount and thus, prolonging the duration of convulsion. Apart from Ca 2+ ions, MES also facilitates the entry of other positive ions such as Na +, blockade of which can prevent the MES-induced tonic extension. Currently available anticonvulsant drugs such as valproate and phenytoin act by modulation of these ion's channels. On the other hand, potentiation of gamma-aminobutyric acid (GABA) receptors is also reported to protect against MES-induced seizures.

Phenytoin is the major enzyme-inducing AED that stimulate the rate of metabolism of most co-administered AEDs, i.e., Lamotrigine. This involves various CYP enzymes (CYP1A2, CYP2C9, CYP2C19, CYP3A4), UGTs and epoxide hydrolase. The clinical significance of these interactions is usually modest because the consequences of the reduction in serum concentration of the affected AED are compensated by the pharmacological effect of the added co-medication. However, in some cases, seizure control may be adversely influenced.

Sodium Valproate is a broad enzyme inhibitor, including CYPs, UGTs and epoxide hydrolase, and inhibits the metabolism of lamotrigine (glucuronidation), leading to increased serum concentrations of the inhibited drugs and consequently, an increased risk of toxicity. The serum concentration of lamotrigine is increased by Sodium Valproate, as studied, increasing the half-life in animals.

CONCLUSION:

As per the observation the Lamotrigine along with the sodium valproate shows more significant variation than that of the Lamotrigine with the phenytoin when compared with that of the Lamotrigine alone. All the three groups (groups-1,2,3) of drugs shows more variation compared with control group (group-1).

The increased levels of the Lamotrigine in case of Group-3(enzyme inhibitor) may increase the risk of adverse effects, whereas decreased levels of Lamotrigine in case of Group-2 (enzyme inducer) may automatically decrease the antiepileptic activity of Lamotrigine. So, it is fore most important to have therapeutical drug monitoring (TDM) of lamotrigine during its concomitant use throughout the therapy.

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