Proarrhythmogenic Risk Assessment of Lamotrigine in Provocative Rat Model

Thesis submitted in partial fulfilment of the requirement

for the degree of Master of Pharmacy

Under the guidance of

PROF. SANMOY KARMAKAR

Submitted by

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Signature of External

Declaration of Originality and Compliance of Academic Ethics

I hereby declare that this thesis contains literature survey and original research as part of my work on "**Proarrhythmogenic Risk Assessment of Lamotrigine in Provocative Rat Model**". All information in this document have been obtained and presented in accordance with academic rules and ethical conduct. I also declare that as required by these rules and conduct, I have fully cited and referenced all materials and results that are not original to this work.

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Exam Roll Number: M4PHC24005

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Dedicated to

My Loving Parents

and

My Lab-family

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ABSTRACT

Lamotrigine(LTG), an anti-epileptic medication, is prescribed to treat neurological illnesses such as epilepsy and bipolar disorder. However, the precise mechanism of action in the central nervous system remains unknown. Recent research indicates that LTG modifies voltage-gated ion channels, reducing neuronal excitability. It also has neuroprotective properties, perhaps blocking glutamate release while increasing GABAergic neurotransmission. LTG's unique mechanism suggests that it might be used to treat various CNS illnesses such as neuropathic pain, PTSD, and major depressive disorder. It has been taken with other medications including mood stabilizers to improve its therapeutic properties. LTG's ability to affect various neurotransmitters and ion channels makes it an attractive candidate for treating neurological diseases. Hypokalemia, also a frequent electrolyte issue, has been shown to impair arrhythmogenic situations. This study looks at the proarrhythmogenic potential of LTG in a rat model with hypokalemia and pharmacologically induced arrhythmias. In this study, adult male Wistar rats were separated into two groups: control and experimental. Dietary modification caused hypokalemia, and an arrhythmogen was injected to cause cardiac arrhythmias. The experimental groups were given varied dosages of LTG. ECG records were utilized to monitor heart rhythm and detect arrhythmias.

The results showed that LTG treatment in hypokalemic rats resulted in a dose-dependent increase in arrhythmic events as compared to control groups. The combination of hypokalemia and arrhythmogen exposure reduced the proarrhythmogenic effects of LTG, resulting in substantial changes in ECG parameters such as longer QT intervals and an increased incidence of ventricular tachycardia and fibrillation.

These data indicate that LTG may enhance the incidence of arrhythmias in individuals with hypokalemia, particularly when exposed to arrhythmogenic situations. This study emphasizes the importance of closely monitoring electrolyte levels and cardiac function in patients using LTG, particularly those who are susceptible to arrhythmia. When prescribing LTG, healthcare practitioners should exercise caution and evaluate cardiac risks, especially in individuals with pre-existing cardiovascular diseases.

CHAPTER-I

INTRODUCTION

INTRODUCTION

Cardiac arrhythmia, also referred to as cardiac dysrhythmia or irregular heartbeat, encompasses a range of heart conditions characterized by abnormal heart rhythms. These irregularities can manifest as either a decrease or increase in the resting heart rate. Clinical terms such as bradycardia and tachycardia are used to describe reduced and increased heart rates, respectively. While many arrhythmias may not pose a significant clinical concern, some can escalate into critical situations such as stroke or heart failure. One notable arrhythmia with severe implications is Torsade's de pointes, a polymorphic ventricular tachycardia that has the potential to result in sudden cardiac death. Initially identified by Dessertenne in 1963, Torsade's de pointes is characterized by a distinct ECG pattern often accompanied by a prolonged QT interval. The term itself, which translates to "twisting of points" in French, aptly captures the erratic nature of this condition. If left untreated, Torsade's de pointes can progress to life-threatening arrhythmias, highlighting the importance of timely intervention and management strategies. It is crucial for healthcare professionals to recognize the unique features of Torsade's de pointes and other serious arrhythmias to provide appropriate care and prevent adverse outcomes. (Viskin et al., 2003) Advances in heart monitoring technologies, such as machine learning algorithms and wearable devices, have revolutionized arrhythmia detection by enabling real-time monitoring, early intervention, and improved diagnostic precision, ultimately enhancing patient outcomes and transforming cardiovascular care. (Kadiyala et al., 2023). By understanding the workings and risk factors associated with these conditions, healthcare providers can implement measures to mitigate potential risks, leading to more effective treatment approaches and improved patient results. (Portela et al., 2014). Ongoing studies and advancements in this field play a crucial role in enhancing the diagnosis and treatment of arrhythmias, underscoring the importance of continuous innovation in heart monitoring technologies for superior patient care on a global scale. (Kadar et al., 2023)

In recent decades, there has been a notable increase in awareness regarding electrolyte abnormalities and their significant association with arrhythmias, particularly after acute myocardial infarction (AMI). Studies have highlighted the prevalence of electrolyte disturbances, such as potassium, calcium, and magnesium imbalances, as crucial predictors for arrhythmias post-AMI (Clinical Research Development Unit (CRDU), Sayad Shirazi Hospital, Golestan University of Medical Sciences, Gorgan, Iran et al., 2023). At a dose of 10 mg.kg-1, the frequently prescribed potent diuretic furosemide (FUR) notably decreased blood potassium

levels in male Wister rats used in trials. According to Akita et al higher doses of FUR may put lab rats at danger for metabolic alkalosis. Thus, in order to reduce the danger of alkalosis, we believe it is probably suitable to utilize our dose of FUR to produce experimental hypokalemia in the animals stated before. Drug-induced QT interval prolongation is a significant concern in clinical practice, with over 50 non-cardiac drugs identified to prolong the QT interval, potentially leading to life-threatening arrhythmias. Various classes of medications, including antimicrobials, have been associated with QT prolongation and subsequent arrhythmias. (Parsons, 2022). The oral macrolide antibiotics, including clarithromycin (CLA), have been extensively studied for their propensity to prolong the QT interval and induce arrhythmias, particularly torsades de pointes (TdP) (Wong et al., 2016). Since QT/QTc is an alternative tool for arrhythmogenesis identification, regulatory bodies have developed preclinical and clinical methods to evaluate the risk of QT prolongation by non-cardiac drugs, leading to the implementation of cardiac assessment tests by the US-FDA in 2005 for new chemical entities (NCEs).

While evaluating novel compounds that may cause arrhythmias in clinical trials prior to commercialization is the primary goal of these guidelines, previously approved drugs that did not account for these concerns at the time of approval are always a source of concern. It is our opinion that in this instance, a "strong safety margin" is associated with an ECG prolonged QT/QTc interval. Biliczki's findings included the observation that cardiac myocyte electrophysiology retained a "strong safety margin." He states that a complex network of interconnected channels closely regulates ventricular repolarization. In repolarization settings, failure is typically due to repolarization reserve rather than impairment or blockage of one kind. However, he demonstrated that proarrhythmic lengthening of the ventricular APD occurs if this repolarization reserve is reduced by total potassium current suppression. Our earlier studies showed that, whereas giving FUR (10 mg kg-1) and CLA (80 mg kg-1) separately did not significantly alter QTc, doing so in combination did produce a noticeable alteration in QT interval. Here, we believe that we can reduce the so-called "strong safety margin" by purposefully inducing hypokalemia by the use of a titrated dose of a recognized arrhythmogen. It was therefore interesting to look into the potential impact of a test agent on repolarization once the safety margin was reduced. Moreover, we believed that the test medicine may exacerbate the experimental animals' reduced QT prolonging tendencies, which are otherwise undefinable by the existing techniques. (Akita et al., 1998)

CHAPTER-II

LITERATURE REVIEWS

LITERATURE REVIEWS

Torsade's de Pointes (TdP), a potentially lethal rhythm, is linked to the extended QT interval, which occurs often. While the inherited variety can occur spontaneously, a number of drugs have been linked to an extension of the QT interval. Some of these drugs have been taken off the market or put under limitations due to the increase of fatal polymorphic ventricular tachycardia. You may get a current list of certain drugs that lengthen the QT interval at reliable medicines. The number of drugs that cause QT prolongation is constantly growing. The primary subjects of this study include the mechanism of drug-induced QT prolongation, risk factors for TdP, offending medications, deterrent and observation of extended drug-induced QT elongation, and treatment methods.

2.1 Cardiac Conduction of Heart:

The cardiac conduction system plays a crucial role in regulating the heartbeat by coordinating the generation and propagation of electrical impulses throughout the heart (Dakhlallah & Manders, 2024). It ensures that the heart contracts in a coordinated manner, allowing it to effectively pump blood throughout the body (Mikawa & Hurtado, 2007). An outline of the cardiac conduction system is provided here.

The sinoatrial (SA) node, the heart's natural pacemaker located in the right atrium, plays a crucial role in initiating the cardiac electrical impulse that triggers atrial contraction (Scheinman, 1993). This impulse spreads through the atria, leading to their contraction and the subsequent blood flow into the ventricles. Subsequently, the electrical signal travels to the atrioventricular (AV) node, where a slight delay occurs, allowing the ventricles to fill completely before contracting (Inada et al., 2017). The impulse then passes through the bundle of His, splits into the bundle branches on the left and right, and continues on its path to the heart's apex. Ultimately, it diffuses across the Purkinje fibers, inducing apical to lateral ventricular contraction and effective blood ejection into the pulmonary and systemic circulation. Maintaining proper heart function depends on this complex electrical conduction process. (Mikawa & Hurtado, 2007)

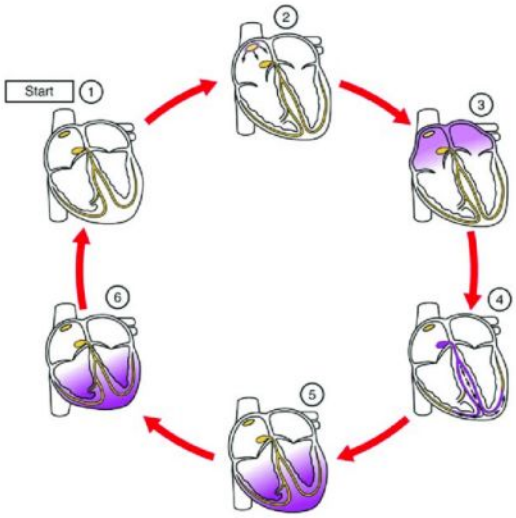


Fig-1: Cardiac Conduction

2.1.1 Nodal Tissue Electrophysiology

The resting membrane potential of pacemaker (SA node) fibers indeed fluctuates between -55 and -60 mV due to a gradual depolarization process, taking a considerable amount of time to reach the threshold level of -40 mV . Once this threshold is met, there is a rapid depolarization of up to 5 mV, followed by quick repolarization, leading to action potential generation . After fast repolarization, the resting membrane potential in phase 4 of the action potential slowly rises again, preparing for the next impulse . (Dokos et al., 1996)

2.1.2 Ionic Insights into SA Node Function: Pacemaker and Action Potential Generation

Depending on the membrane potential, the form, and the conduction velocity of the action potential, the cardiac cells found in the SA node and AV node are referred to as slow fibers.

a. A distinctive characteristic of the pacemaker tissue's slow fibers is that their resting membrane leaks sodium ions (as opposed to the resting membrane of fast fibers, which is mostly resistant to Na^+). Under resting conditions, this results in a gradual diffusion of Na^+ into the SA nodal fibers. Because non-selective channels are present, the slow entrance of Na^+ into the cells gradually elevates the potential to -55 mV (causing slow depolarization). The first portion of the pacemaker potential is formed by this gradual depolarization. Due to their unique activation during hyperpolarization, which is linked with enhanced permeability to both sodium and potassium, nodal tissues also have some funny (f) channels. However, sodium conductance has the dominating influence. These

channels are also known as "h" channels since become active when the membrane is hyperpolarized (between -40 and -60 mV).

b. After then, the 'T' (transient) calcium channels open, allowing a sluggish inflow of Ca^{2+} to cause additional depolarization at a slower pace, up until a threshold level of -40 mV is achieved. The latter portion of the pacemaker potential is therefore formed by the calcium current (Ica) brought on by the opening of "T calcium channels.".

c. When the "long lasting calcium channels" open at the threshold level (-40 mV), the action potential begins with a fast depolarization caused by an influx of Ca^{2+}. It is crucial to remember that Ca^{2+} rather than Na^{+} is the primary cause of the depolarization in the SA node. As a result, the depolarization is less abrupt than it is in other cardiac fibers.

d. Calcium channels close and potassium channels open as depolarization comes to an end. K^{+} diffuses out of the fibers as a consequence, causing a fast repolarization to between -55 and -60 mV.

e. Once more, because of the special property of the SA node's slow fibers (leaking of the resting membrane to Na^{+}), the resting potential does not become stable. Instead, gradual depolarization begins as a result of the slow inflow of Na^{+}, which forms the initial portion of the prepotential. And finally, new action potential is started as a result of repeating the previously outlined stages. In this approach, impulses (autorhythmicity) are produced at regular intervals of time (Baruscotti et al., 2010).

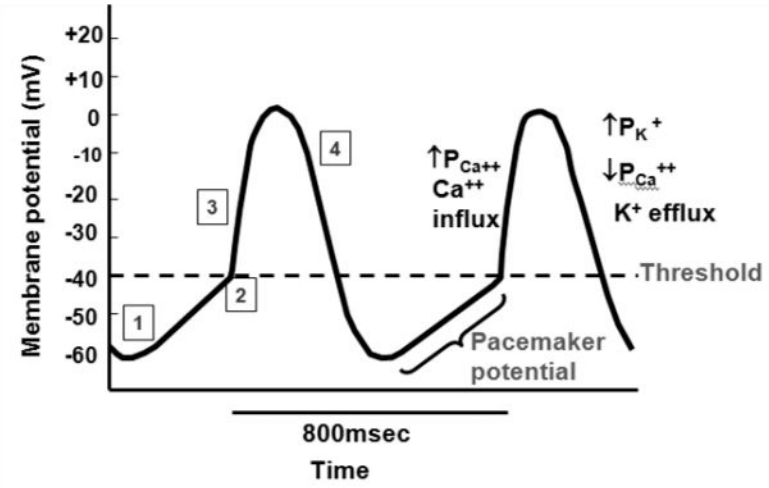


Fig 2: Electrophysiology of Pacemaker potential

1. 'Funny' sodium channels (I_f channels) are open (P_{Na^+}); and closing K^+ channels. 2. Transient Ca^{2+} (T-type) channels open, pushing the membrane potential to threshold. 3. Long-lasting Ca^{2+} (L-type) channels open, giving rise to the action potential. 4. Opening of channels, (P_{K^+}), and closing of Ca^{2+} (L-type) channels, hyperpolarising the cell.

2.1.3 Electrophysiology of cardiac muscle:

2.1.3.1 Resting membrane potential.

A typical cardiac muscle fiber's resting membrane potential (RMP) ranges from -85 to -95 mV (negative interior with respect to outside).

2.1.3.2 Action potential:

The action potentials (APs) in cardiac myocytes are orchestrated by the conduction system, originating from specialized pacemaker cells that generate electrical signals propagating through the heart in a coordinated fashion. These APs consist of five distinct phases (Phase 0 to Phase 4) regulated by various ion channels present in the sarcolemma, crucial for the generation and propagation of the cardiac action potential(Vornanen et al., 2024).

a. Phase 0: Rapid depolarization:

The depolarization of adjacent cells through gap junctions plays a crucial role in the initiation of systole (Carmeliet, 2019). During the upstroke phase (phase 0) of the action potential in mammalian hearts, rapid depolarization occurs due to the quick opening of voltage-gated sodium channels, leading to a rapid influx of Na^+ ions, similar to what happens in nerve and skeletal muscle cells. This phase typically lasts around 2 ms and can exhibit a potential amplitude of 20 to 30 mV (positive interior with respect to the outside). Additionally, calcium channels open at membrane potentials of -30 to -40 mV, allowing the influx of Ca^{2+} ions, which also contributes to the depolarization and overshoot observed during this phase (Schmitt et al., 2014)

b. Phase 1, Transient repolarization phase

The brief repolarization that causes the transient outward potassium current, or IK to, to be activated and the sodium channels to become inactive that causes the transient repolarization phase. The membrane potential fluctuates between +30 mV and -10 mV throughout this phase.

Ionic basis. Na^+ channel closure and K^+ channel opening cause the initial rapid repolarization, which results in a transient outward current (Amin et al., 2010)

c. Phase 2, Plateau:

Throughout the plateau stage, the heart muscle fibre remains depolarized. The membrane potential only gradually drops to -40 mV throughout this period. The duration of the plateau

period is 100–200 ms. This action potential plateau may be the cause of the cardiac muscle contraction time being 5–15 times longer than that of skeletal muscle.

Ionic basis. The slow pace inflow of Ca^{2+} ions brought on by the opening of sarcolemma L type Ca^{2+} channels and the closure of a particular subset of K^+ channels known as the inward rectifying K^+ channels are the two causes of the plateau phase's extremely slow repolarization (Schmitt et al., 2014).

d. Phase 3:

Repolarization: In this phase, repolarization takes place. It occurs when ICa, L is inactivated and IKur, IKr, and IK1 are increased. In these phase the membrane potential drops to around 80 mV, which is the resting state. This phase lasts for about 50 ms (Schmitt et al., 2014).

Ionic basis: In addition to the contribution of the slow potassium current (IKs) and the inward rectifying potassium current (IK1), increased the conductance of the fast potassium current (IKr) and the deactivation of calcium channels result in complete repolarization.

There are two types of rectifying K^+ channels: rapid delayed rectifying K^+ channel (IKr) and slow delayed rectifying K^+ channel (IKs). IKr is responsible for initial phase of phase 3 repolarization, whereas late phase of phase 3 repolarization is controlled by IKs.

e. Phase 4:

Phase 4 represents the cell's resting potential.

Resting potential: In this phase of RMP (also called as polarized state), the potential is maintained at −90 mV.

Ionic basis: The inward rectifying K^+ current is the principal contributor to the resting K^+ current, which maintains the RMP (Miake et al., 2003).

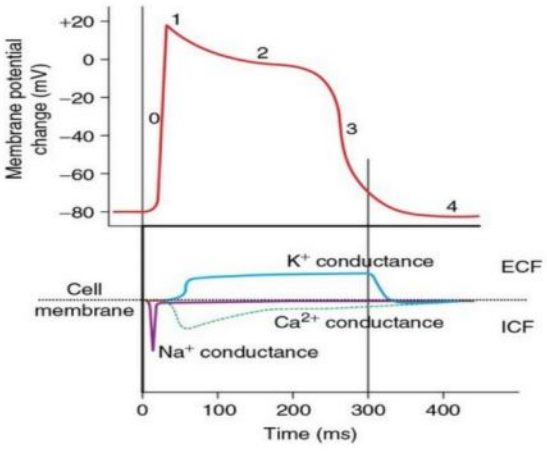


Fig 3- Various phases of action potential and ion conductance:

Phase 0 = depolarization; Phase 1 = rapid repolarization; Phase 2 = plateau phase; Phase 3 = late rapid repolarization and Phase 4 = resting potential.

2.1.3.4 Duration of action potential:

An action potential, mostly repolarization, at a heart rate of 75 beats per minute lasts for around 250 milliseconds. The action potential's length (150 ms at 200 beats per minute) shortens with an increase in heart rate. It is shorter in the atrial muscle. The cardiac myocyte cells in the ventricles contain action potentials with a fast response.

2.2 Physiology of the QT interval and the mechanism of QT drug-induced prolongation:

An electrocardiogram (ECG) is a crucial diagnostic tool for monitoring heart function and detecting cardiac diseases, providing a graphical representation of the heart's electrical activity (Sree et al., 2023). It is a graphical representation of the electrical activity of the heart. The QT-interval, a significant ECG parameter, measures the duration of ventricular depolarization and repolarization, starting from the QRS complex to the T wave's end. Prolongation of the QT-interval can lead to Torsades de Pointes (TdP), a life-threatening arrhythmia This interval serves as a marker for long QT syndrome (LQTS), characterized by an abnormally prolonged QT-interval on the ECG, often caused by dysfunction in cardiac ion channels affecting ventricular repolarization associated with sudden cardiac death, particularly in young individuals. This interval serves as a marker for long QT syndrome (LQTS), characterized by an abnormally prolonged QT-interval on the ECG, often caused by dysfunction in cardiac ion channels affecting ventricular repolarization (Sanguinetti & Jurkiewicz, 1990).

IKr, IKs, and Na protein channel gene mutations cause congenital long QT syndrome (LQTS). In acquired LQTS, the inward potassium rectifier (IKr) channel—also called the hERG (ether a go go) channel—is almost always blocked. It is responsible for the fast delayed rectifier potassium current (IKr), which is necessary for the cardiac action potential's phase 3 repolarization. Congenital alterations (loss of function) in the hERG gene cause type 2 LQTS. Drugs that extend the QT interval have an impact on the same hERG channel. Because of its distinct molecular makeup, the hERG channel is more susceptible to drugs (Roden, 2005).

2.2.1 The structure of the hERG channel:

Voltage-gated sodium channels (NaV) are crucial transmembrane proteins responsible for controlling the flow of sodium ions across cell membranes, particularly in muscle and nerve tissues (Weinberg, 2023).

To date, nine mammalian NaV isoforms have been identified and functionally expressed (NaV1.1, NaV1.2, NaV1.3, NaV1.4, NaV1.5, NaV1.6, NaV1.7, NaV1.8 and NaV1.9)

Voltage-gated sodium (NaV) channels consist of a highly processed α-subunit (260 kDa) and one or more minor auxiliary β-subunits (33–37 kDa), with the β-subunits playing a crucial role in modulating NaV gating kinetics, voltage dependence, channel expression, signal transduction, and cell adhesion. The α-subunit, comprising four homologous domains (DI-DIV) with six α-helical transmembrane segments (S1–S6) each, is essential for channel function, including ion selectivity and voltage sensitivity. The S4 transmembrane segments of the α-subunit act as voltage sensors, similar to other voltage-gated ion channels, regulating channel gating (Catterall et al., 2023),(Perry et al., 2010). Four of them, one from each subunit, form a central pore that regulates the potassium current's flow. A center hollow is created by the pore opening up beneath the selectivity filter. Its inside is lined with several unique aromatic residues that are absent from most other K channels. These well positioned polar and aromatic residues are crucial for the unique binding sites of different pharmacologic agents . Pentamidine, fluoxetine, and arsenic oxide are a few examples of drugs that can interfere with KCNH2 protein trafficking and result in K channel loss. The SCN5A channel can be restored by cisapride, which also increases the inward sodium current. Calcium current inward can be increased by antimony (Perrin et al., 2008).

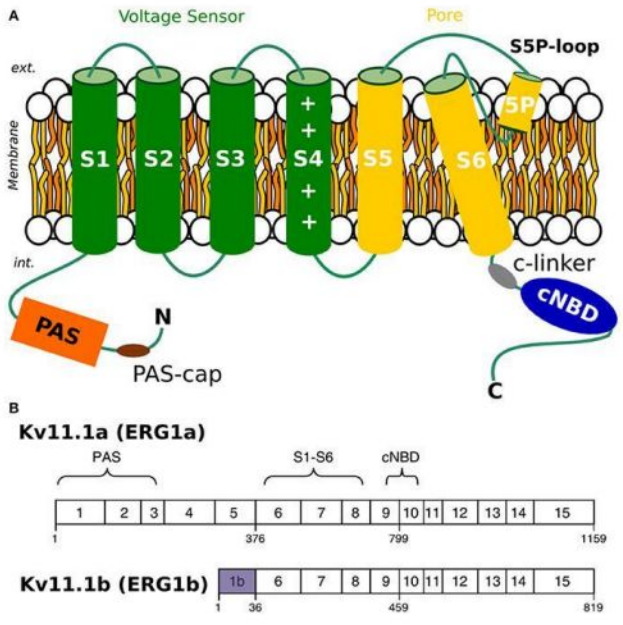


Fig- 4 Structure of hERG Channel

Table 1: Cardiac potassium (K+) channels in human cardiomyocytes include:

Sl. No	Types of K^+ channel	Function
1	Transient outward K^+ current (I(to1))	This channel contributes to the early phase of repolarization of the cardiac action potential.
2	Ultra-rapidly activating delayed rectifier current (IKur)	This channel is primarily found in atrial myocytes and contributes to the repolarization of the atrial action potential
3	Rapidly and slowly activating delayed rectifier currents (IKr) and I(Ks)	These channels contribute to the late phase of repolarization of the cardiac action potential.
4	Inward rectifier K^+ current (IK1))	This channel helps to maintain the resting membrane potential of the cardiomyocyte.
5	Adenosine-5'-triphosphate (ATP)-sensitive K^+ current (IKATP)	This channel is activated during metabolic stress, such as ischemia, to shorten the action potential duration and reduce energy consumption.
6	Acetylcholine-activated current (IKACh)	This channel is activated by acetylcholine and contributes to the slowing of the heart rate during parasympathetic stimulation.

2.2.2 Repolarization reserve

The concept of repolarization reserve, as highlighted in the research papers, refers to the heart's capacity to maintain repolarization under various challenges, such as genetic mutations, drugs, or environmental factors, ultimately influencing the development of arrhythmias. If one current is affected others can Provide a capacity for repolarization acting as a "reserve". Studies emphasize that cardiac ion currents can compensate for each other, contributing to a robust repolarization reserve that prevents lethal arrhythmias. By optimizing ion-channel conductances, particularly by increasing repolarizing current conductances, the heart can enhance its repolarization reserve and resist arrhythmogenic insults (Roden, 2006) . Iks channel has greater responsibility for maintaining the repolarization reserve. Under normal physiologic conditions, IKs do not significantly contribute to Phase 3 of repolarization. However, during conditions like increased sympathetic stimulation or blocked IKr, the current passing through this channel increases. Thus, IKs provide a repolarization reserve or a physiologic check to prevent excess action potential duration lengthening and QT prolongation. This current is defective in Long QT syndrome type 1. This current is more active in the epicardial and endocardial cells and intrinsically weak in the M cells. However when this reserve is diminished the risk of arrhythmias increases. Repolarization reserve plays a role in conditions such as Long QT syndrome where there can be QT prolongation due to genetic or environmental factors. When the repolarization reserve is reduced in these cases it heightens the chances of developing arrhythmias (Varró & Baczkó, 2011). On the other hand, arrhythmia risk rises when this reserve is reduced. In diseases such as Long QT syndrome, where QT prolongation may be brought on by environmental or hereditary causes, repolarization reserve is important. In these situations, a decrease in the repolarization reserve increases the risk of arrhythmia development.

According to research, people with heart defects often have a lower repolarization reserve than people in good health who don't have any cardiac problems (Kang et al., 2022). Furthermore, research has shown that humans generally have a lower repolarization reserve than dogs, highlighting the ways in which species-specific characteristics affect how much repolarization a person may achieve (Jost et al., 2013). It becomes essential to comprehend the idea of repolarization reserve when thinking about drug-induced proarrhythmia. Certain drugs may interfere with one or more cardiac currents, causing the heart to repolarize. Drug disruption can result in arrhythmias if a person's preexisting repolarization reserve is inadequate (Varró & Baczkó, 2011).

2.2.3 Transmural dispersion of repolarization and T wave generation:

Transmural dispersion of repolarization (TDR) across the ventricular wall, as indicated by data from various studies, is defined by the differences in repolarization time (activation time +action potential duration (APD) between the M cell and the epicardial cell. The morphology of the T wave is influenced by opposing transmural currents generated by voltage gradients during repolarization, particularly between the epicardium and the M-cell region and between the M-cell region and endocardium. The magnitude of these currents is regulated by the high tissue resistivity between the epicardium and the M area. In an ECG, the end of the T wave aligns with the repolarization of the longest M-cell action potential, while the peak of the T wave corresponds to the repolarization of the shortest epicardial action potential, highlighting the intricate relationship between transmural repolarization gradients and T wave morphology. Endocardial action potential repolarization typically falls somewhere between that of M cells and that of epicardial cells. On the other hand, the duration of repolarization of the subendocardial Purkinje fibers is always greater than that of the M cells, suggesting that Purkinje cell repolarization does not contribute to the manifestation of T waves. The three electrically distinct cell types found in the ventricular wall—the epicardium, endocardium, and T wave morphologies—interacted to produce the various T wave morphologies. It was postulated that LQTS results from the preferential prolongation of M cells by ion channel mutations, which also contributes to long QT intervals and TdP. They are known to have electrical characteristics and drug response patterns consistent with the ECG signs of long QT and TdP development (Maffessanti et al., 2017).

2.3 Typology of Long QT Syndrome

LQTS can be classified in following type Congenital and acquired.

Table 2: Mutations inion-channel genes causing Long QT syndrome.

Genotype	Chromosome	Affected gene	Channel protein	Ion channel current	Reference
LQT1	11	KCNQ1 (Kv7.1)	4-α subunits each with 6 membrane spanning segments	↓ I_{Ks}	(Zareba & Cygankiewicz, 2008)

LQT2	7	KCNH2 (hERG) (Kv11.1)	4-αsub units each with 6 membrane spanning segments	↓I_{Ks}	(Zareba & Cygankiewicz , 2008a)
LQT3	**3**	SCN5A (Nav1.5)	1-subunitwith 24membrane spanning segments	↑Late I_{Na}	(Zareba & Cygankiewicz , 2008)
LQT4	4	Ankyin-B (ANK2)	Sodium pump and Na/Ca exchanger		(Zareba & Cygankiewicz , 2008)
LQT5	21	KCNE1 (MinK)	Alpha-subunitof KCNQ1with1 membrane spanning segment	↓I_{Ks}	(Zareba & Cygankiewicz , 2008)
LQT6	21	KCNE2 (MiRP1)	Alpha-subunitof KCNH2with1 membrane spanning segment	↓I_{kr}	(Zareba & Cygankiewicz , 2008a)
LQT7	17	KCNJ2 (Kir2.1)	2membrane spanning segments	↓I_{K1}	(Zareba & Cygankiewicz , 2008a)
LQT8	12	CACNA1C (Cav1.2)	1 1-subunitwith 24membrane spanning segments	↑I_{Ca}	(Mohamed et al., 2024)
LQT9	3	CAV3 (Caveolin)	Altered gating kinetics of Nav1.5		(Zareba & Cygankiewicz , 2008a)
LQT10	11	SCN4B (NavB4)	Alpha-subunitof SCN5Awith1 membrane spanning segment	↑ Late I_{Na}	(Zareba & Cygankiewicz , 2008a)

2.3.1 Congenital LQTS

Congenital long QT syndrome (LQTS) is a hereditary arrhythmic disorder characterized by a prolonged QT interval on ECG, leading to a risk of fatal arrhythmias like torsades de pointes and sudden cardiac death. It affects approximately 1 in 2000 individuals, can manifest in more than ten distinct ways. with mutations in genes like KCNQ1, KCNH2, and SCN5A accounting for about 90% of cases, categorized into LQT1, LQT2, and LQT3 subtypes (Balestra et al.,

2024). 40-55% of instances of the LQTS are caused by LQT1. Exercise-induced events are what make LQT1 unique. 35–45% of congenital LQTS instances are caused by LQT2 (Schwartz et al., 2001), (Splawski et al., 2000) It is caused by several mutations in the chromosome 7 potassium channel gene hERG, sometimes referred to as KCNH2. The mutations may impact the pore or nonpore portion of the hERG channel. While pore mutations have a high risk of cardiac events and can affect younger patients, nonpore mutations often cause Torsade's de Pointes (TdP) in the setting of hypokalemia. 8-10% of cases are explained by LQT3. The disorder is caused by the sodium channel gene SCN5A, which is located on chromosome 3 at locations 21–24. It is defined by things that happen to you while you're sleeping or at rest (Hedley et al., 2009).

2.3.1.1 LQT1:

LQTS1 is triggered by a loss of function KCNQ1 (potassium voltage-gated channel, KQT-likesubfamily,member1) gene mutation that causes a decrease in outward potassium current during Phase2,which leads to a delay in ventricular depolarization and a prolongation of QT interval on ECG. .KCNQ1is the alpha-subunit of the voltage-dependent potassium channel responsible for the slow component of the delayed rectifier current IKs (Splawski et al., 2000)

Chromanol 293B, a moderately selective IKs blocker, has been shown to mimic the LQT1 state by uniformly prolonging the action potential duration (APD) across the ventricular wall without widening the T wave or increasing the T wave dispersion (TDR) (Pugsley et al., 2015).In contrast, beta-adrenergic stimulation with isoproterenol enhances transmural repolarization attenuation by reducing the APD of epicardial and endocardial cells, leading to total QT wave prolongation without affecting the M-cell ceiling. Isoproterenol is expected to increase residual IKs more in epicardial and endocardial cells than in M cells, where IKs are naturally weaker, resulting in a shorter response in the former but not the latter, potentially causing a broad T wave and increased TDR (Schwartz et al., 2001).

2.3.1.2 LQT2

The KCNH2 gene, which encodes the alpha-subunit of the IKr channel and is also known as the human Ether-a-go-go-Related Gene, is the origin of loss-of-function mutations that result in Long QT syndrome type 2 (LQTS2) (Shimizu & Antzelevitch, 2000).

D-Sotalol, an IKr blocker, can mimic acquired types of Long QT Syndrome (LQTS) and LQT2 by preferentially elongating the M-cell action potential duration (APD).It significantly slows down phase 3 repolarization across different cell types, leading to a prolonged QT interval,

increased transmural diffusion of repolarization, and characteristic small amplitude T waves with a deeply notched or bifurcated appearance commonly observed in LQT2 patients (Shimizu & Antzelevitch, 2000).

2.3.1.3 LQT3

ATX-II, a substance mimicking the LQT3 state by increasing late sodium current (INa), significantly prolongs the QT interval and broadens the T wave, inducing a rapid increase in the T-wave dispersion ratio due to its impact on M-cell action potential duration (APD). This delay in T-wave generation aligns with the delayed T-wave pattern observed in LQT3 syndrome, as ATX-II affects both epicardial and endocardial APD. While ATX-II lengthens the APD, substances like SGLT2 inhibitors and SGK1 inhibitors have shown efficacy in shortening APD in LQT3 models, suggesting potential therapeutic avenues for counteracting the effects of ATX-II-induced APD prolongation (Diness et al., 2009).

2.3.2 Acquired LQTS:

Acquired long QT syndrome (aLQTS) is primarily caused by exogenous stressors like medications, electrolyte imbalances (eg, Hypokalemia, Hypomagnesemia etc), hypothermia, and various cardiac conditions (eg, hypertension, congestive heart failure, ischemic cardiomyopathy, left ventricular hypertrophy). Genetic variations may influence a person's propensity to acquire acquired QT interval prolongation (Mahida et al., 2013). With the exception of individuals with congenital LQTS, the estimate of 35% heritability of QT interval duration in the general population supports this (Hong et al., 2001). First-degree relatives of patients with congenital long QT syndrome (LQTS) have a higher likelihood of experiencing drug-induced QT prolongation, indicating a genetic predisposition to this condition (Behr et al., 2003). The nitric oxide synthase 1 adapter protein gene (NOS1AP), which is located on chromosome 1 (1q23.3) and inhibits L-type calcium channels and affects impulse propagation, has the largest correlation with QT interval duration (Behr et al., 2003). Subsequent GWAS findings included congenital mutations in the LQTS gene, variations in genes related to intracellular calcium handling, and previously unidentified genes influencing cardiac repolarization. Compared to over a thousand people with hereditary LQTS, only 28% of patients with drug-induced LQTS were found to have disease-causing mutations in a recent study. Notably, under baseline conditions, the QTc of individuals with drug-induced LQTS (45339 ms) was significantly longer than that of control participants (40626 ms) (Itoh et al., 2016). It is important to consider the pharmacogenetics of drug-induced LQTS in connection to the pharmacokinetic and pharmacodynamic aspects of the condition. Pharmacokinetics

involves the body's response to medications, encompassing drug distribution, absorption, metabolism, and elimination (Moini et al., 2023). Genetic variations in drug-metabolizing enzymes and transporters significantly impact individual responses to pharmacological treatments, leading to inter-individual variability in drug effectiveness and tolerability (Kerb, 2006). Pharmacogenomics plays a crucial role in uncovering these genetic differences, with a focus on genes encoding drug-metabolizing enzymes and transporters involved in drug absorption, distribution, metabolism, and excretion (ADME) (Arbitrio et al., 2018). Mutations in genes encoding cytochrome P450 enzymes and drug transporters like P-glycoprotein are key factors determining genetic vulnerability in pharmacokinetics, while genes associated with QT prolongation in the general population and congenital long QT syndrome (LQTS) influence pharmacodynamic genetic susceptibility. These genetic variations play a significant role in tailoring treatment approaches for precision medicine based on individual genetic factors (Vafiadaki et al., 2010), (Itoh et al., 2016).

Table 3: Drugs, responsible for acquired LQTS:

Drug Class (with Known Risk for TdP)	**Drug**	**Molecular Mechaanism for Prolong QT Interval**	**Reference**
Anticancer	Arsenictrioxide	Inhibition of Kv11.1 trafficking	(Vafiadaki et al., 2010)
	Vandetanib	Downregulation of hERG channel expression	(Cui et al., 2022)
Antiarrhythmic	Amiodarone	IKr block, binds to the closed state of the channel	(Mourad et al., 2018)

	Disopyramide	IKr block,INa,	(Mourad et al., 2018)
	Dofetilide	IKr block, INa-L	(Tisdale et al., 2020)
	Flecainide	IKr block Inhibition of CYP3A4	(Osadchii, 2012)
Antihistaminic	Astemizole	IKr block	(Zhou et al., 1999)
	Terfenadine	IKr block	(Chen et al., 2019)
Antibiotic	Azithromycin	INa-Loading	(Zhou et al., 1999)
	Sparfloxacin	IKr block	(Zünkler et al., 2006)
	Clarithromycin	IKr block Inhibition of CYP3A4	(Stanat et al., 2003)
	Erythromycin	IKr block,INa-L augmentation Inhibition of CYP3A4	(Stanat et al., 2003)
	Gatifloxacin	IKr block	(Frothingham, 2001)
	Moxifloxacin	IKr block	(Khan et al., 2018)

Antimalarial	Chloroquine	IKr block ,	(Delaunois et al., 2021)
	Hydroxychloroquine	IKr block,	(Jankelson et al., 2020)
Antidepressant	Citalopram	IKr block, and Inhibition of Kv11.1 trafficking	(Ojero-Senard et al., 2017)
	Escitalopram	IKr block, and Inhibition of Kv11.1 trafficking.	(Ojero-Senard et al., 2017)
Anaesthetic	Propofol	IKr block, Ito block	(S.-N. Han et al., 2016)
	Sevoflurane	IKr block, Ito block	(Yamada et al., 2003)
Antiemetic	Domperidone	IKr block,	(Claassen & Zünkler, 2005)
	Ondansetron	IKr block	(Danielsson et al., 2018)
Antifungal	Fluconazole	IKr block,and Inhibition of Kv11.1trafficking	(S. Han et al., 2011)

GI stimulant	Cisapride	Downregulation of hERG channel expression	(Walker et al., 1999)

2.3.3 Role of Potassium in developing LQTS:

Potassium is on of the vital electrolyte which is required for functioning of cardiac myocytes. In case of low level of potassium or hypokalemia; serum potassium (K^+) levels lower than 3.5 mM. It can be classified as mild (3.0–3.5 mM), moderate (2.5–3.0 mM), and severe (<2.5 mM) (Alfonzo et al., 2006). QT prolongation and an increased risk of arrhythmias can arise from disruptions in the sensitive equilibrium of ionic currents required for prompt cardiac repolarization, which can be caused by mutations in genes involved for the formation of potassium channels or hypokalemia. Hypokalemia has a vital role in both congenital and acquired LQTS. Increased ventricular action potential duration (APD) and a longer QT interval on the electrocardiogram (ECG) are signs of prolonged ventricular repolarization. The suppression of outward K^+ currents that contribute to ventricular repolarization is thought to be the cause of the lengthening of APD in a hypokalemic environment. Hypokalemia has been seen to significantly reduce the conductance of IKr, the fast component of the delayed rectifier, in isolated guinea-pig ventricular myocytes (Sanguinetti & Jurkiewicz, 1992). The enhancement of the quick inactivation that the IKr experiences following depolarization explains these alterations. (Yang et al., 1997). The time constant for the rapid inactivation of IKr is shortened by hypokalemia, indicating that a decrease in extracellular K^+ concentration speeds up the channel's transition from an open to an inactivated state. Chronic hypokalemia promotes internalization of plasma membrane IKr channels, thereby reducing their cell surface density.

The propensity for early after depolarizations increases when ventricular repolarization is prolonged because more time is spent across the voltage window for the reactivation of inward Na^+ and Ca^{2+} currents. Early afterdepolarizations result in ventricular-triggered beats that have the potential to start a prolonged tachyarrhythmia if they reach a threshold voltage level (Killeen et al., 2007). When hypokalemia is coupled with other treatments that prolong APD, such as bradycardia, hypomagnesemia, and some anti-arrhythmic medications (e.g., quinidine or d-sotalol), the likelihood of early afterdepolarizations is noticeably enhanced (Zabel et al.,

1997). Hypokalemia decreases the ERP in the atrial muscle (Bertrix et al., 1984), and it may also exacerbate the contraction associated with the refractory period induced by acetylcholine. Due to the shortened excitation wavelength caused by these modifications, tachyarrhythmia susceptibility is increased (Tse et al., 2021). After an early extra systolic stimulation, the delayed after depolarizations amplify with rapid cardiac pacing and may result in prolonged triggered activity. Due to activation of the reversed mode of the Na^+–Ca^{2+} exchange due to increase of intracellular Na^+ levels coming from blockage of the Na^+–K^+ pump by hypokalemia, the delayed afterdepolarizations of cardiac myocytes are produced by Ca^{2+} overload (Eisner & Lederer, 1979).

2.3.4 Risk Factors for Acquired Long QT Syndrome:

TdP is a rare event that usually occurs in patients with predisposing risk factors. The most well-established risk factors include female sex, electrolyte imbalances, age more than 65, structural cardiac disease, bradycardia, renal failure, concurrent use of two or more QT prolonging medications, genetic predisposition, and diabetes (Kallergis et al., 2012), (Chorin et al., 2020).

Table 4: Risk factors associated with prolonged QTc (Kallergis et al., 2012)

System	Risk Factor
Autonomic nervous system	Pheochromocytoma, Head-up-tilt, Pure autonomic failure, Sleep deprivation.
Cardiovascular disease	Bradycardia, Stress cardiomyopathy, Stroke Aortic stenosis.
Electrolyte disorders	Hypokalemia, Hypomagnesemia, Hypocalcemia, Gitelman syndrome, Blood transfusion.
Endocrine disorders	Hypothyroidism Hyperparathyroidism
Environmental effects	Hypothermia, Carbon monoxide, Grapefruit juice, Synthetic cannabinoids.
General	Female sex, age > 65,
Inflammation/auto-immune	Rheumatoid arthritis Inflammation/auto-immune Celiac disease, Ankylosing spondylitis.

Miscellaneous	Genotypic association, Propionic academia, Liquid protein diet, Sickle cell disease.

2.3.5 Measurement of the QT interval:

The QT interval on a 12-lead ECG is the distance between the start of the QRS complex and the end of the T wave as it returns to baseline. Leads II and V5 or V6 should be used to manually measure the QT interval, with the longest value being chosen. When it comes to identifying aberrant QT intervals, measurements made from these leads have the highest positive and negative predictive values (Mönnig et al., 2006). At least three to four cardiac cycles should be used to get the mean value. At least three to four cardiac cycles should be used to get the mean value. The junction point between the tangent formed at the highest downslope of the T wave and the iso electric line serves as a reliable indicator of the end of the T wave according to the slope technique. If the T wave is notched, the greatest slope should get the tangent. While bigger U waves that merge with T waves should be included in the measurements, smaller U waves (0.1 mV) should be removed (Anderson et al., 2001). The interpretation of extended QT intervals from Holter or 24/48 h ambulatory monitoring recordings is not standardized. As a result, ambulatory QT assessment monitoring is not advised. The QT interval is influenced by a number of variables, including gender, heart rate, underlying rhythm, and conduction abnormalities. The patients' physiologic and metabolic states have an impact as well. There are several methods for adjusting QT intervals for heart rate, and each has advantages and drawbacks of its own. There is no agreement on which is the most efficient. However, Bazett's calculation ($QTc = QT/\sqrt{RR}$ in seconds), which offers a sufficient correction for heart rates ranging from 60 to 100 beats per minute, is the one that is most frequently used. However, for low and high heart rates, it, respectively, underestimates and overestimates the QT interval. Other correction techniques, such as Fredericia ($QTc = QT/(RR)1/3$) or Framingham ($QTc = QT + 0.154(1 - RR)$), should be used for heart rates beyond the normal range(Karjalainen et al., 1994). These techniques of adjustment, however, do not take into account intra- or inter-individual variability because they are based on the population mean correction factor. The optimal HR adjustment for QT should be computed for each individual as there is now substantial evidence for significant inter-individual variability. The procedure of estimating each individual correction factor is laborious and time consuming. Although it is recommended in clinical research, it cannot be used in actual clinical settings. Based on a QT-RR cloud diagram created from human preclinical investigations(Smetana & Malik, 2013), Fossa and

associates offered a QT-HR nomogram that is easily used in the clinical context. The nomogram, which uses HR rather than RR interval, has been found to be secure, to have great sensitivity, and to be sufficiently precise to allow the identification of many patients as "not at risk" for drug-induced TdP and, as a result, to not need cardiac monitoring(Chan et al., 2007) Bateman looked explored how well the nomogram performed in individuals who had taken an excessive number of antidepressants but did not have arrhythmia. Comparing the QT nomogram to other frequently used QTc criteria, a reduced false-positive rate was found. Patients with heart rates between 30 and 60 beats per minute showed the highest disparity between the nomogram and QTc techniques. In contrast to venlafaxine and mirtazapine overdose, individuals with citalopram overdoses had QT values above the nomogram, indicating a greater risk of developing an arrhythmia and the need for vigilant cardiac monitoring(Waring et al., 2010). According to Bazett's corrected QTc value, a QT interval in adult men that is larger than 450 ms is regarded as protracted, while one that is between 430 and 450 ms is regarded as borderline. According to Goldenberg et al. (2006), a QT interval in females more than 470 ms is regarded as protracted, while one between 450 and 470 ms is regarded as borderline.

Table 5. Methodologies for correcting QT intervals

Correction	Formula
Bazzet	$QTc = QT/\sqrt{RR}$
Fredericia	$QTc = QT/(RR)1/3$
Framingham	$QTc = QT + 0.154(1 - RR)$

2.3.6

Uncovering the Mechanisms of TdP in LQTS:

Prolonged QT interval, as observed in cases of Long QT syndrome (LQTS) induced by medications like selective serotonin reuptake inhibitors and antipsychotics, can lead to a higher risk of polymorphic ventricular tachycardia, such as Torsades de Pointes (TdP), which can result in sudden cardiac death (SCD). This dangerous arrhythmia can be triggered by early after depolarization (EAD) oscillations, which may lead to ectopic beats and subsequent reentrant excitation, especially when the myocardium's action potential duration is significantly varied,

potentially resulting in TdP . (El-Sherif et al., 1999). This short-long-short cycle onset pattern is typical of drug-induced TdP, also known as pause-dependent TdP. On the other hand, TdP often follows a sudden adrenergic spike, such as that caused by exercise or alertness, in the congenital form. Whatever the mechanism, TdP frequently stops on its own without lasting very long. Yet if it continues, ventricular fibrillation and SCD might develop (Passman & Kadish, 2001).

2.3.7 Genomic Risk Factors for LQTS

Indeed, according to Paulussen et al.'s study in 2004, in approximately 5-20% of patients who developed drug-induced Torsades de Pointes, underlying genetic mutations predisposing to Long QT Syndrome could be found. These subjects generally had, therefore, baseline QTc intervals related to normal or borderline values, but with a compromised cardiac repolarization reserve and hence became more susceptible to QT prolongation and TdP when challenged with specific medications. Genetic variations in the activity of the CYP2D6 enzyme may further decrease drug metabolism, increasing the risk of QT prolongation and TdP. Genetic polymorphisms that render the majority of White patients poor metabolizers increase their risk for cardiac adverse events with therapies that involve the use of medications known to prolong QT intervals. (Bradford, 2002).

The hERG blockade risk assessment can be facilitated by calculating the EPTC/IC50 ratio, also referred to as the therapeutic index. This ratio represents the balance between the effective plasma therapeutic concentration (EPTC) and the in vitro concentration required to inhibit 50% of hERG activity (IC50). The higher the ratio, the higher the risk of Torsades de Pointes. In fact, some drugs with a ratio of more than 1, like cisapride, sparfloxacin, quinidine, ibutilide, thioridazine, and so on, should be given with caution for their ability to cause hERG-mediated arrythmia. (De Bruin et al., 2005).

2.4 Drugs That Increase LQTS Susceptibility

The incidence of drug-induced Torsades de Pointes (TdP) in the general population remains largely elusive, as it is influenced by diverse factors such as demographic characteristics and pharmacological agents. However, a notable observational study revealed that approximately 3.1% of patients receiving non-cardiac medications developed TdP. Furthermore, a comprehensive compilation of medications with potential QT-prolonging effects is provided in the accompanying box, underscoring the complexities of this phenomenon.

2.4.1 Antiarrhythmic agents:

The preponderance of drug-induced Torsades de Pointes (TdP) cases can be attributed to antiarrhythmic medications, particularly Class IA agents, which concomitantly inhibit sodium (Na) and potassium (K) channels. Quinidine, procainamide, and disopyramide exemplify this category, capable of precipitating TdP even at therapeutic or subtherapeutic concentrations. Quinidine, for instance, typically elicits a 10-15% prolongation of the QT interval within a week of initiation, entailing a 1.5% risk of TdP (Darpo, 2001). The likelihood of TdP is further augmented by hypokalemia or hypomagnesemia during antiarrhythmic treatment, which doubles the mortality risk when employed for rhythm maintenance in atrial fibrillation. Procainamide, with its primary Na blocking action, is less predisposed to inducing TdP, although its active metabolite, N-acetyl procainamide (NAPA), can precipitate TdP in individuals with renal impairment or rapid acetylators due to its potent K blocking effect. Disopyramide has also been implicated in TdP and is contraindicated in patients with hepatic, renal, or cardiac dysfunction. Furthermore, Class III drugs, which inhibit the IKr channel, exhibit a dose-dependent QT prolongation, highlighting the intricate relationship between pharmacological agents and TdP risk. The inverse usage-dependent property of potassium channel blockade renders it most pronounced at low heart rates (Hondeghem & Snyders, 1990). Among antiarrhythmic agents, amiodarone exhibits the lowest propensity for inducing Torsades de Pointes (TdP), followed by dofetilide, ibutilide, and sotalol. According to Lehmann et al. (1996), sotalol is associated with a 2-4% incidence of TdP, with female patients demonstrating increased susceptibility. Torp-Pedersen et al. (1999) reported a 2.1% incidence of dofetilide-induced TdP, with a heightened risk in patients with renal insufficiency. Stambler et al. (1996) found that intravenous ibutilide carries a 1-3% risk of TdP, with a greater incidence in patients with structural heart disease, heart failure, and electrolyte disturbances. Notably, amiodarone rarely precipitates TdP, despite its QT-prolonging effects, which can be attributed to its unique pharmacological profile, including a lack of reverse usage dependence, reduced QT dispersion across the ventricular myocardium, and its effects on L-type calcium channels and blocking actions(Riera et al., 2008).

2.4.2 Antihistamines

Non-sedating antihistamines are commonly prescribed, despite the fact that only a limited number of medications have been implicated in significant arrhythmogenic potential. Astemizole and terfenadine, formerly available antihistamines, were withdrawn from the market due to their potent inhibitory effects on the IKr channel, even at low doses, which

predisposed patients to Torsades de Pointes (TdP). Most of the antihistamines are mainly metabolically degraded by the cytochrome P450 enzyme CYP3A4. However, elevated drug concentrations can result in patients with hepatic impairment or after co-administration of CYP3A4 inhibitors with other drugs or ingested with certain foods, increasing the potential for adverse cardiac events. Although the pro-arrhythmogenic propensity of newer non-sedating antihistamines remains uncertain, they appear to exhibit a reduced arrhythmogenic potential compared to their predecessors(Dagenais et al., 2001).

2.4.3 Antiemetics

This class of antiemetics, which are 5-hydroxytryptamine type 3 receptor antagonists, has been shown in vitro to have an inhibitory action on both the IKr and cardiac sodium channels, thus leading to variable prolongations in the QRS and QTc intervals, mostly with intravenous use, at high doses, or in patients having elevated risk profiles. Notably, ondansetron, at standard perioperative doses (4 mg, 0.15 mg/kg), and to a lesser extent, granisetron and dolasetron, have been implicated in QTc prolongation (Benedict et al., 1996). In accordance with guidelines from the Federal Drug Administration, patients with congenital long QT syndrome (LQTS) are contraindicated from receiving ondansetron; electrolyte imbalances must be corrected prior to administration; and patients with congestive heart failure, bradyarrhythmia, or those concurrently receiving other QTc-prolongating agents necessitate electrocardiographic monitoring (Charbit et al., 2005).

2.4.4 Atypical antipsychotics

Case reports and the FDA adverse event reports have implicated atypical antipsychotics in the development of Torsades de Pointes, thus associating them with a risk of QTc interval prolongation. Though ziprasidone has been shown to result in the longest QT prolongation, olanzapine has been associated with the least. Notably, in 1998, sertindole was withdrawn from the market due to an increased risk for its induction of TdP and sudden cardiac death. Furthermore, citalopram and zimelidine have been implicated in TdP at hazardous concentrations(Liljeqvist & Edvardsson, 1989)

2.4.5 Antidepressants

Compared to SSRIs, Prolongation of the QTc interval is more common with TCAs. The main mechanism of this phenomenon is the blockade of sodium channels, which prolongs QTc. Concurrent administration of potassium channel blocking agents may further exaggerate this effect. According to Casazza et al. (1986), several TCAs, including amitriptyline, desipramine,

and imipramine, have been implicated in Torsades de Pointes (TdP). At toxic concentrations, TCAs can induce a range of electrocardiographic alterations, including QRS complex widening, QT prolongation, and TdP. On the other hand, some studies have also linked QT interval prolongation to the use of SSRIs like escitalopram and citalopram. This is essentially through the blockade of the IKr channel. (Ray et al., 2004).

2.4.6 Antipsychotic

Classic antipsychotic medications are generally known to cause Torsades de Pointes and prolong the QT interval in a dose-dependent way. Haloperidol is a butyrophenone derivative, used in the management of severe agitation and schizophrenia, and is considered a very potent inhibitor of the IKr channel, causing a prolongation in the QT interval of 15–30 ms. (Glassman & Bigger, 2001). The presence of risk factors amplifies this effect. In 2007, the United States Food and Drug Administration (FDA) issued a warning recommending electrocardiographic (ECG) monitoring during intravenous administration of haloperidol. However, based on available evidence, it is considered safe to administer intravenous haloperidol to patients without risk factors up to a cumulative dose of 2 mg without ECG monitoring (Meyer-Massetti et al., 2010). Effects of haloperidol and droperidol are similar, with closer monitoring indicated in those patients with risk factors. Chlorpromazine has both antipsychotic and antiemetic effects and has been associated with QT prolongation and TdP due to its blocking effects on the potassium channel, similar to thioridazine.

2.4.7 Antibiotics

Specifically, macrolide antibiotics, especially clarithromycin and erythromycin, have been associated with torsades de pointes and prolongation of the QT interval. Animal studies have shown that erythromycin has class III antiarrhythmic-like actions, such as transmural dispersion and prolongation of the QT interval. Since both erythromycin and clarithromycin have been shown to be inhibitors of CYP3A4, they can produce adverse effects either as single agents or in combination with other inhibitors/substrates for CYP3A4. Although considered safe, azithromycin has also been linked to TdP (Anderson et al., 2002).

Fluoroquinolones exhibit varying effects on the QTc interval, with TdP being a rare adverse event. Grepafloxacin and sparfloxacin significantly delay repolarization, whereas gatifloxacin, levofloxacin, and moxifloxacin have a lesser impact on the IKr channel (Anderson et al., 2001). The remaining fluoroquinolones are generally safe, but caution is warranted in the presence of risk factors or concurrent QT-prolonging medication.

Antimalarial drugs are commonly prescribed worldwide, but the true incidence of QT prolongation and TdP associated with their use remains largely unclear due to underreporting.Quinine, the optical isomer of quinidine, has little or no QT-prolonging effect and only seldom causes TdP. The antimalarials halofantrine and chloroquine have both been associated with TdP and prolongation of the QT interval; halofantrine has class III antiarrhythmic effects in vitro similar to those of quinidine and the class III antiarrhythmic drugs. (Wesche et al., 2000).
Pentamidine's electrophysiologic properties are unclear, but its structural similarity to procainamide is notable. Intravenous administration can lead to TdP, whereas inhaled use is considered safe (Eisenhauer et al., 1994).

Systemic azole antifungal medications possess pharmacologic and pharmacokinetic characteristics that may induce TdP, necessitating cautious use, especially in individuals with underlying QT prolongation risk factors (Owens, 2004).

2.4.8 Other agents

Cisapride, a gastrointestinal prokinetic agent, inhibits both IKr and IKs channels and has a structure similar to procainamide (Carlsson et al., 1997). Wysowski et al., 2001 suggested that Its use was associated with a higher incidence of TdP than antiarrhythmic medications, leading to its withdrawal from the US market in July 2000.

2.5 Electrocardiographic Screening for LQTS:

During the drug development, it has become a conventional practice to conduct hERG channel functionality assessments during the preclinical safety evaluation phase, given the considerable risk of QT prolongation and Torsade's de Pointes (TdP) associated with various pharmacological agents. One of the most important elements in this practice is the "thorough QT/QTc study," a study of rigorous design that can identify medications with very great confidence that have the ability to prolong QT interval. This has become an integral part of research and development programs for new molecular entities.
A thorough QT/QTc study is a randomized, double-blinded model drug study enrolling a placebo and positive control arms with a well-powered design to detect an effect on QTc interval > 10 ms, which would be conducted in healthy volunteers after the establishment of the drug's pharmacokinetics and tolerability.
All measures of electrocardiographic intervals, including RR interval, cardiac rate, and QT interval, are recorded with care, and the latter is rate-corrected using both Bazett's and

Fridericia's corrections: QTcB = QT/RR0.5 and QTcF = QT/RR0.33. ECG interval measurement techniques are either fully manual or subject to manual adjudication to ensure that the results are highly accurate.

The positive control is a benchmark to provide sensitivity for the detection of even a modest QT change, e.g., prolongation of about 5 ms in duration. A very small QT effect with the test drug would indicate that the drug does not importantly prolong the QT, under the assumption that if it did, then the study had the power and methods to detect a small effect, similar in size to that of the positive control. Moxifloxacin is a fluoroquinolone antibiotic with a mild QT-prolonging effect that has been used as an active comparator in the thorough QT studies. Bloomfield et al., 2008 proposed that estimated mean increase in the placebo- and baseline-corrected QTc interval of 7.5-12.5 ms for moxifloxacin 400 mg supports its use as a positive control in TQT studies.

Typically, QT studies yield three clinical outcomes: (1) the investigated medication prolongs the mean QTc interval by approximately 10 ms without inducing Torsades de Pointes (TdP) or exhibiting a negligible risk; (2) the examined medication causes a mean QTc interval prolongation of >10 ms but <20 ms, resulting in an uncertain probability of TdP induction; and (3) the investigated medication increases the mean QT/QTc interval by >20 ms, potentially leading to clinically significant arrhythmic events.

In the event of a "negative" outcome, Phase II-III clinical drug testing can proceed with standard ECG data collection in accordance with conventional protocols. Conversely, Phase II and III studies require additional ECG data to obtain comprehensive dose-response information and achieve a "nonnegative" outcome (QTc interval >10 ms).

Individuals with additional risk factors for Torsades de Pointes (TdP), including those with electrolyte imbalances (e.g., hypokalemia), congestive heart failure, impaired drug metabolism or clearance (e.g., renal or hepatic impairment, drug interactions), as well as female patients and those aged 16 and above 65 years, must be encompassed in these analyses to comprehensively assess the risk of QT prolongation.

Recent investigations have demonstrated that fully or partially automated methods of QT interval measurements, leveraging computer algorithms, yield comparable results to manual methods when evaluating drugs with a known QT-prolonging effect (Fosser et al., 2009). The integration of automated QT algorithms is expected to supplant manual QT measurements and

enhance the detection of subtle T-wave variations in the evaluation of novel pharmacological agents (Darpo, 2010).

2.6 The treatment of TdP:

The efficacy of therapeutic interventions is significantly influenced by hemodynamic stability. In instances where Torsades de Pointes (TdP) fails to spontaneously resolve or progresses to ventricular fibrillation, prompt direct-current cardioversion is warranted. Conversely, for individuals exhibiting stable hemodynamics, the following management strategies can be employed:

- ✓ In the context of Long QT Syndrome (LQTS)-associated Torsades de Pointes (TdP), administration of an intravenous (IV) or intraosseous (IO) bolus of magnesium sulphate, ranging from 25-50 mg/kg (with a maximum dose of 2 g), is recommended over a duration of 2-3 minutes (or extended to 10-20 minutes in stable patients with palpable pulses). A subsequent bolus, followed by an infusion if necessary, should be considered 10-15 minutes later. Magnesium's stabilizing effect on the cardiac membrane is thought to be mediated by its modulation of sodium, potassium, and calcium channels, thereby reducing the incidence of arrhythmic events (Hyman & Kaplan, 1985).
- ✓ Given that intravenous potassium administration has been observed to mitigate QT interval abnormalities during the acute phase, with a dosage range of 0.5 meq/kg up to a mean total of 40 meq, its consideration is warranted even in individuals exhibiting normokalemia.
- ✓ In cases where intravenous magnesium is applied and the patient does not show any improvement, overdrive transvenous pacing is another option. This method aims to maintain a heart rate between 90 and 110 beats per minute. Through this method, several trials have shown that there was a marked decrease in the number of EADs and QT dispersion, which consequently shortened the QT interval. (Rosenberg et al., 2005).
- ✓ In those instances when Torsades de Pointes is provoked by bradycardia or pauses, temporary overdrive pacing or isoproterenol may be considered as a therapeutic option.
- ✓ Careful scrutiny of the medication list is necessary to identify potential QT-prolonging offenders. (crediblemeds.org) offers a good and up-to-date resource that provides data on medications associated with QT prolongation.

- ✓ Permanent pacemaker implantation is entertained in patients with chronic bradycardia, specifically those with AV block or sick sinus syndrome. ICDs are proposed for use in people for whom avoidance of the offending agent is not possible.

2.7 Monitoring and Mitigating Drug Induced QT Prolongation

For instance, those who have a personal history of ventricular arrhythmias or pre-existing cardiac conditions should not use medications that lengthen the QT interval. Another risk group is hospitalized patients, people usually over sixty years old and most of whom have some form of underlying heart disease. They are more likely to have Torsades de Pointes because the bradycardia, electrolyte disturbances, and impaired renal function that can exacerbation TdP are present in this patient population. When necessary, such as with hypokalemia, medication might need to be given intravenously immediately. Avoid taking macrolide antibiotics and imidazole antifungals - both cytochrome P450 inhibitors - concurrently. With ECG monitoring, for both diuretics and all other medications that lengthen the QT interval, patients should have an ECG both before starting therapy and at regular intervals thereafter. Routine electrolyte testing is also recommended, especially testing for potassium ions.

Methadone in females has been associated with TdP at doses exceeding 100 mg/day. Approximately a million Americans use methadone to treat drug addiction or as an analgesic. Procedures currently require a pretreatment ECG measuring the QTc interval, an ECG within 30 days of initiation, and one each year thereafter, following guidelines. (Materson & Caralis, 1984).

In a clinical setting, electrocardiogram (ECG) monitoring of the QT interval is warranted in the following scenarios: initiation of medications known to precipitate Torsades de Pointes (TdP); overdose of potentially proarrhythmic substances; new-onset bradyarrhythmias; and severe electrolyte imbalances, specifically hypokalemia or hypomagnesemia. A close look at the patient's own and family health records is crucial when dealing with drug-caused TdP to rule out inherited Long QT Syndrome (LQTS). Also close family members of people with unexplained fainting or sudden unexpected death in their personal or family history should get a 12-lead ECG. What's more, doctors should think about using available genetic tests for inherited LQTS keeping in mind how the patient's symptoms look and their family's health background.

CHAPTER III

TEST DRUG PROFILE

Introduction

Anticonvulsants, also known as antiepileptic drugs, are drugs that are given to the patient to either prevent or treat seizures. This is achieved by altering the activity of some neurotransmitters in the brain, which play a role in seizure generation and propagation. AEDs terminate an abnormal electrical activity of the brain that causes seizure by modifying the neurotransmitter functions(Löscher & Klein, 2021). Early in the 1980s, LTG (LTG) was first synthesized. In 1990, the UK authorized it for adult usage, and in 1994, the US Food and Drug Administration (FDA) gave it approval (Weisler et al., 2008). Ever since its market authorization over two decades ago, it has been used increasingly for the treatment of paediatric epilepsy. It is the most commonly prescribed new generation . This makes it, at present the most frequently prescribed antiepileptic drug, accounting for 65% of new AED prescriptions in the UK. This represents 12% of all AED prescriptions for children in the Netherlands alone(Van De Vrie-Hoekstra et al., 2008). In the UK, monotherapy with lidocaine (LTG) is advised as the initial course of treatment for recently identified focal seizures and as a support for children with refractory focal seizures.
It is monotherapy in the second line medication for generalized seizures with a recent start and a helpful adjuvant for refractory generalized epilepsy. After ethosuximide and valproate, it is the third medication of choice for absence seizures and it can be used either as a polytherapy or as a monotherapy(National Clinical Guideline Centre (UK), 2012). LTG employs a more complex mechanism of action involving the blocking of both sodium and N- and L-type calcium channels as well as the modulation of H-current(Ketter et al., 2003).

Chemistry and Structure:

LTG is a member of the class of 1,2,4-triazines in which the triazene skeleton is substituted by amino groups at positions 3 and 5, and by a 2,3-dichlorophenyl group at position 6. Its molecular formula and molecular weight is C9H7Cl2N5 and 263.09g/mol respectively. It is having a solubility of 0.17mg/ml and 4.1mg/ml at 25ºC in water and 0.1M HCl respectively with pKa of 5.7. White to pale cream-colored powder. Crystals from isopropanol.

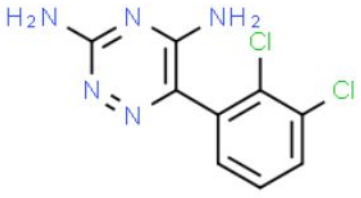


Fig 5. Chemical structure of LTG

Mode of action:

LTG helps to normalize the presynaptic neuronal membranes by modulation of voltage-dependent sodium channels, and excitatory neurotransmission, inclusive of aspartate and

glutamate. In-vitro studies on rat cerebral cortex revealed that lag could prevent veratrine, a sodium channel activator aspartate, glutamate, and was found to be much less effective in the inhibition of GABA or acetylcholine release is not altered by potassium-induced amino acid release. In conclusion, therefore, has been suggested to act pre-synaptically on voltage-sensitive sodium channels. (Leach et al., 1986) Another study in mouse neuroblasts blocked repetitive and sustained firing of sodium-dependent action potentials suggest a direct effect on voltage-activated sodium channels. (Helen et al., 1992). By this LTG inhibits the release of certain neurotransmitters in the brain, such as glutamate and aspartate (Abelaira et al., 2012). everal studies have reported an increase in GABA levels in brain tissue and synaptic fluid following LTG treatment, as well as a decrease in seizure activity. In addition, LTG has been shown to increase the release of the inhibitory neurotransmitter GABA, resulting in further reduction of excitability that leads to seizures. Although the effects of GABA modulation by LTG are not particularly strong, they occur consistently even outside of seizure activity. They may contribute to some of the psychotropic effects of LTG (Brodie et al., 2016)

In addition to its established mechanisms of action, LTG has been shown to modulate HCN channels and inhibit glutamate release, as well as possess antioxidant and neuroprotective properties, all of which contribute to its efficacy in treating these disorders and potential use in other conditions. HCN channels, also known as hyperpolarization-activated cyclic nucleotide-gated channels, are ion channels that drive pacemaker currents in neurons and cardiac cells. LTG has been demonstrated to modify HCN channels in a variety of ways (Postea & Biel, 2011) First, it can directly block HCN channels, lowering pacemaker current and delaying neuron firing rates (Kessi et al., 2022). Second, it can increase the sensitivity of HCN channels to cyclic nucleotides, lowering neuronal excitability (Poolos, 2010),(Kessi et al., 2022). LTG's regulation of HCN channels may have an impact on illness outcomes and side effects. For example, LTG's lowering of neuronal excitability may be advantageous in the treatment of epilepsy and bipolar illness, where excessive neuronal activity can contribute to seizures and mood instability (Kessi et al., 2022)

Furthermore, LTG's regulation of HCN channels may have an influence on brain processes other than epilepsy and bipolar illness, such as learning and memory, sleep, and pain. LTG controls HCN channels and has been demonstrated to influence intracellular calcium signalling by suppressing calcium ion release from intracellular storage and decreasing calcium ion influx through voltage-gated calcium channels (VGCCs). Reducing calcium inflow can affect the

calcium-dependent signalling pathways regulated by HCN channels. (Kessi et al., 2022), (Ku & Han, 2017)

Pharmacokinetics and Pharmacodynamics

LTG's pharmacokinetics have been studied in various settings, including epileptic patients, healthy volunteers, and those with chronic renal failure. It is rapidly absorbed after oral administration, with an absolute bioavailability of 98%. Peak plasma concentrations occur between 1.4 and 4.8 hours after administration, increasing in proportion to the dose. The mean apparent volume of distribution ranges from 0.9 to 1.3 L/kg. LTG is 55% bound to human plasma proteins and is metabolized predominantly by glucuronic acid conjugation. The elimination half-life and apparent clearance depend on whether the patient is receiving enzyme-inducing drugs. If stopping LTG is necessary, it should be done gradually over two weeks. LTG is metabolized in the liver by glucuronidation and oxidation, being mainly metabolized by UGT enzymes in the body and excreted by the kidneys, with CYP enzymes not participating in its metabolism having a half-life of 15–30 (Milosheska et al., 2016)

The mechanism by which it crosses the blood-brain barrier is not completely understood, but studies have shown that organic cation transporters may play a role. There is conflicting evidence for the role of ABC transporters, such as P-glycoprotein and ABCG2, in LTG efflux across the blood-brain barrier. Polymorphisms in these genes have been associated with differences in LTG concentrations in plasma, which may explain differential drug response. LTG is extensively metabolized, with over 80% of the total dose recovered in the urine as glucuronides and primarily eliminated by ABCC transporters (Mitra-Ghosh et al., 2020)

Therapeutic Dosage

The appropriate LTG dose varies with the patient group. The suggested beginning dosage for individuals with epilepsy is 25 mg once day, followed by moderate increments of 25-50 mg every one to two weeks until the desired therapeutic impact is attained. The maintenance dose is usually 100-200 mg per day. (Matsuo et al., 1996). The suggested beginning dosage for pediatric patients is 0.6 mg/kg per day, with incremental increases of 0.2-0.3 mg/kg per day every one to two weeks until the desired therapeutic effect is attained (Besag et al., 1995). Pediatric patients often get a maintenance dose of 5-15 mg/kg per day. In individuals with bipolar illness, the suggested beginning dose is 25-50 mg per day, progressively increasing by 25-50 mg per week until the desired therapeutic effect is reached. The maintenance dosage is typically 200–400 mg per day (Shah et al., 2017). It is important to note that LTG should be

taken with caution in patients with liver or kidney dysfunction and in those who are pregnant or breastfeeding (Jang et al., 2021).

Interaction

Carbamazepine (CBZ) and phenytoin increase LTG metabolism, reducing serum half-life from 15-35 hours to 8-20 hours (Biton, 2006). One of the most widely utilized combinations is LTG plus valproate (VPA), which has a shown synergistic effect. However, VPA can reduce LTG clearance by 54% in combination therapy and 21% in triple therapy with CBZ, causing skin rash and possibly deadly Stevens-Johnson syndrome. Furthermore, CBZ and LTG use in combination treatment may be associated with a greater prevalence of neurotoxic side effects.

Combining LTG with other broad-spectrum AEDs, such as levetiracetam (LEV) or tocopheryl phosphate mixture (TPM), may be possible because these medications do not affect LTG clearance (Lee & Dworetzky, 2010). Finally, it is important to highlight that rifampicin, a strong inducer of various drug-metabolizing enzymes such as CYPs and uridine-diphosphate glucuronosyltransferase (UGT), can lower LTG levels (Wimpelmann et al., 2019). Oral contraceptives, especially estradiol, significantly reduce serum/plasma levels of LTG, which is processed by the liver's UGT enzymes, which are influenced by natural estrogens including estrogen and ethinyl estradiol. Because of this action, LTG clearance can dramatically rise throughout pregnancy, albeit there is substantial interindividual variability (McMillin & Krasowski, 2016).

Therapeutic Use

LTG (LTG), a broad-spectrum AED that was initially found while researchers looked for phenytoin analogues with less potent anti-folate effect. LTG is similarly effective as carbamazepine (CBZ) or phenytoin (PHT), but it is better tolerated than valproic acid (VLP) and has a more favorable adverse drug reaction (ADR) profile (J. Messenheimer et al., 1998).

LTG in Paediatric Care:

LTG in the treatment of childhood absence seizures: In a retrospective analysis, patients with typical absence seizures refractory to VPA were treated with low-dose of LTG and treatment appeared to be effective. In children and adults, 1.6 – 3mg/kg/day and 25 – 50mg/day of VPA was added to differing doses of LTG. LTG in the treatment of tonic-clonic seizures: In an unblinded randomised controlled trial by SANAD in hospital-based outpatient clinics in UK,

study was aimed to compare the longerterm effects of VPA, LTG, or topiramate in patients with tonic-clonic onset seizures or seizures that are difficult to classify (Ferrie et al., 2009).

Efficacy of LTG in Lennox-Gastaut Syndrome and Juvenile Myoclonic Epilepsy

LTG (LTG) has demonstrated efficacy in managing Juvenile Myoclonic Epilepsy (JME) and seizure activity associated with Lennox-Gastaut syndrome. A randomized, double-blind, placebo-controlled trial investigated the use of LTG as adjunctive therapy in patients with Lennox-Gastaut syndrome, yielding promising results(Motte et al., 1997).

Role and effect in psychiatry

LTG was initially synthesized as an anticonvulsant agent; however, its therapeutic uses soon expanded into the psychiatric arena. In fact, by the late 1990s, LTG had been identified as a mood-stabilizing agent, predominantly for the treatment of bipolar disorders. Actually, numerous trials have confirmed its efficiency in maintaining bipolar stability, thus preventing relapse into both depressive and manic episodes in adults aged 18 years and older. Currently, LTG is licensed for maintenance treatment of bipolar disorder for the prevention of depressive episodes in bipolar II disorder (Cohen et al., 1985).

Role and effect on cognitive function:

Association of anti-epileptic therapy with cognitive impairment represents a particular problem, especially in the young and elderly. Existing data suggest that LTG is an effective, well tolerated new generation AED.

Role and effect on neuronal damage:

Status epilepticus causes neuronal damage and cognitive impairment. In a study on wistar rats for 2 weeks, LTG was compared with CBZ for their effect on status epilepticus-induced temporal lobe damage and memory impairment. Role and effect on women and pregnancy Among all the AEDs and mood stabilisers, CBZ and valproic acid are widely used.

Side Effects

Common CNS side effects of LTG can include drowsiness, headache, dizziness, and ataxia (uncoordinated movements). These side effects are usually mild and go away on their own, but in rare cases, LTG can cause serious CNS side effects such as seizures, confusion, and behavioral changes (Ettinger et al., 1998). In some individuals, LTG can also cause a serious skin reaction known as Stevens-Johnson syndrome (SJS), which can be life-threatening. SJS

can cause skin and mucosal tissue to peel off, and it can also cause severe eye damage (Edinoff et al., 2021). LTG carries a black box warning about aseptic meningitis and life-threatening skin reactions like Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome, toxic epidermal necrolysis (Brodieg, 1994).

CHAPTER IV

AIM & OBJECTIVE

4.1 AIM

- ✓ To explore the proarrhythmogenic potential of LTG in rat model.

4.2 OBJECTIVE

- ✓ To evaluate of LTG effects by measuring certain ECG parameters like- QT interval, RR interval, Corrected QT.
- ✓ To measure serum electrolytes like potassium, magnesium.

CHAPTER-V

PLAN OF WORK

5.1 PLAN OF WORK:

5.1.1 Step I- Literature Review

- Gather comprehensive information on Lamotrigine, hypokalemia, and arrhythmias.
- Review existing studies on Lamotrigine's cardiac effects.
- Study the mechanisms of hypokalemia-induced arrhythmias.
- Investigate models used for studying arrhythmias in rats.

5.1.2 Step II

Lamotrigine purchase from local market.

5.1.3 Step III

Animal Model Preparation.

5.1.4 Step IV

Monitoring and Data Collection.

- Use electrocardiography (ECG) to monitor heart rate and rhythm.
- Record baseline data before and after inducing drugs.
- Continuously monitor rat's post-LTG administration for changes in ECG patterns.

5.1.5 Step V- Biochemical Analysis

- Collect blood sample from each group of rat.
- After that analyzed serum potassium levels to confirm hypokalemia.

5.1.6 Step VI- Data Analysis

- Compare ECG data, serum potassium levels, between control and
- Lamotrigine-treated groups.
- Use statistical methods to determine the significance of observed effects

CHAPTER-VI

MATERIALS & METHODS

6.1 Animals Husbandry and Maintenance -

Healthy adult male Wistar albino rats (8–9 weeks) weighing 140-180gm were procured from West Bengal Livestock Development Corporation Limited. Buddha Park, Kalyani, Nadia-741235. FSSAI REG NO – 10012031000104, and used for the study.

The animals were kept in polypropylene cages with well-aerated stainless-steel covers. All animals were kept in a departmental animal house. Animals were kept under controlled conditions of temperature (12-hour light and dark cycle, temperature of 25 ± 2°C and 50 ± 20 % relative humidity). The studies were approved by the Institutional Animal Ethics Committee. (IAEC: - "JU/IAEC-24/63")

6.2 Drug

The following chemical agents were used: Clarithromycin injection (Klacid IV) from Abbott Healthcare Pvt.Ltd., India; Furosemide injection (Lasix) from Sanofi India Limited; Lamotrigine Tablet (Lametec-25 DT) from Cipla Ltd, India; Ketamine hydrochloride Injection from Vulcan Laboratories, India; Xylazine Injection from Indian Immunological.

6.3 Chemicals-

Magnesium assay kit, Sodium/Potassium/Chloride (ELYTE®3) assay kit were manufactured by Coral Clinical System, India.

6.4Experiment Protocols:

6.4.1 Experiment-I :

Animals were divided into four groups (n=6): Group I (Compromised group) received furosemide (FUR) intra-peritoneal (IP) injection at 1 mg./kg/day and clarithromycin (CLA) IP injection at 50 mg./kg/day; Group II (Compromised +Test drug BD) received FUR IP at 1 mg./kg/day, CLA injection at 50 mg./kg. day-1 and Lamotrigine Oral 2.5 mg./kg/ twice daily; Group III (Compromised +Test drug OD) received FUR IP at 1mg./kg/day, CLA injection at 50 mg./kg and Lamotrigine Oral 2.5 mg./kg; and Group IV (LTG) received only Lamotrigine Oral 2.5 mg./kg/day. After seventh days of above mentioned treatment, blood sample were collected in heparinised tubes under anaesthesia. About 250µl of the collected blood was centrifuged at 850xg for 5 min at 10°C for harvesting plasma and finally plasma was stored at -80°C until analysis.

6.4.2 Measurement of surface electrocardiogram (ECG) recording of anaesthetic rats

Rats were anesthetized using Ketamine (60mg./kg) and xylazine (10mg./kg) according to the method of ECG was recorded for 10 min, 2 h after medication using standard lead II (metal ECG leads). The ECG signals were acquired and analysed by BIOPAC (Biosystems, USA) MP36. ECG tracing on zero day i.e., before administration of drug was considered as self-control while that of the seventh day was compared with the said control. Duration of QT was determined from the onset of QRS complex to the end of T wave. Measured QT was corrected using normalised Bazett's equation to obtain the corrected QT (QTc) interval.

6.4.3 QT correction –

QT interval is highly dependent on the heart rate, while that of rats it varies over a wide range. Accordingly, the measured QT was thus corrected using normalized Bazett's equation $QTc=QT/\sqrt{(RR/f)}$, where f is the normalization factor. In this present study, the normalization factor is the value of the average RR duration of each group.

6.4.4 Analysis of serum electrolyte-

Rat blood samples on zero day i.e., before administration of drug was considered as self-control while that of the seventh day (2 hrs after CLA dose) was compared with the said control. The blood samples were then centrifuged at 2400g for 10 min and serum was separated and were analysed for electrolyte concentration. Serum potassium, magnesium, sodium concentrations were determined using kit.

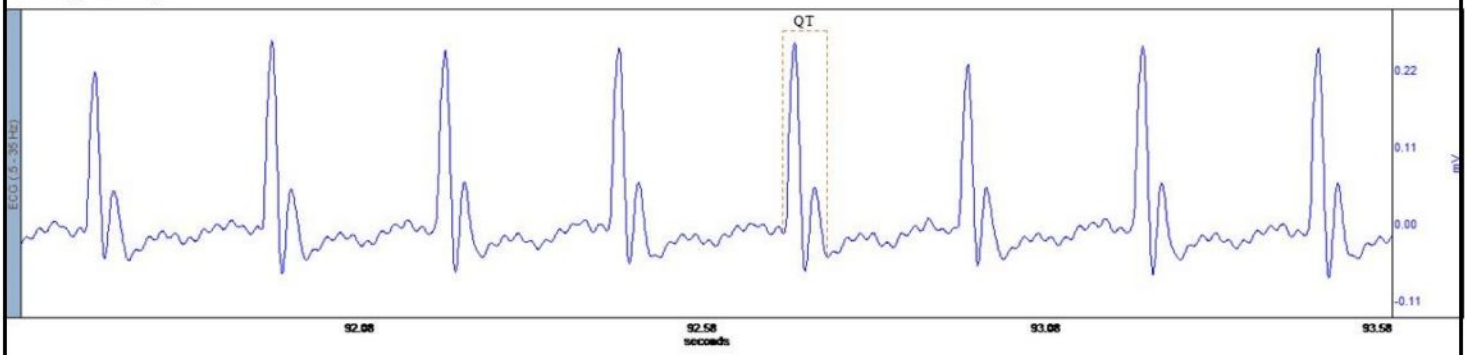
6.4.5 Statistical analysis –

Values are expressed as Mean ±SD (n=6). Statistical analysis was performed using Student's t-test (GraphPad Prism5, USA), *$p< 0.05$ was taken as the criterion of statistical significance.

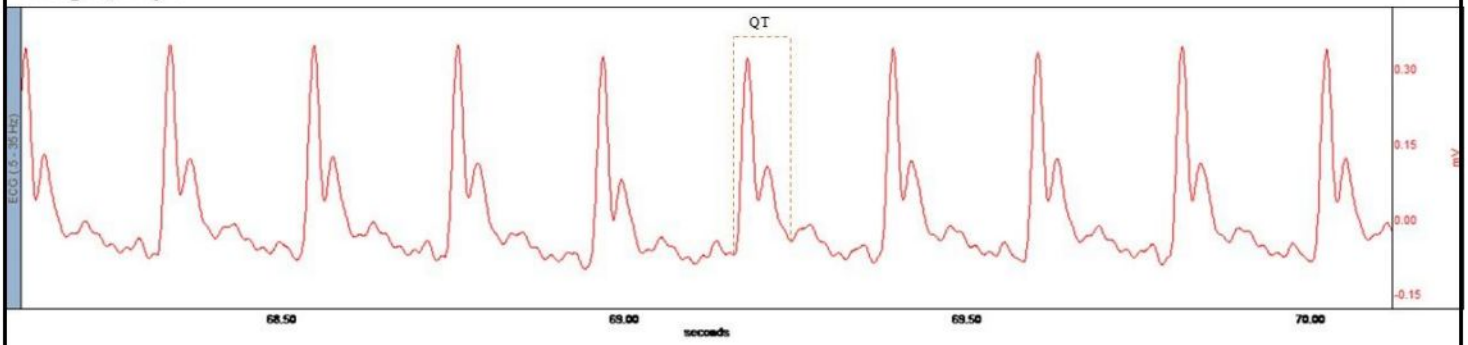
CHAPTER-VII

RESULTS

Group I , Day 0

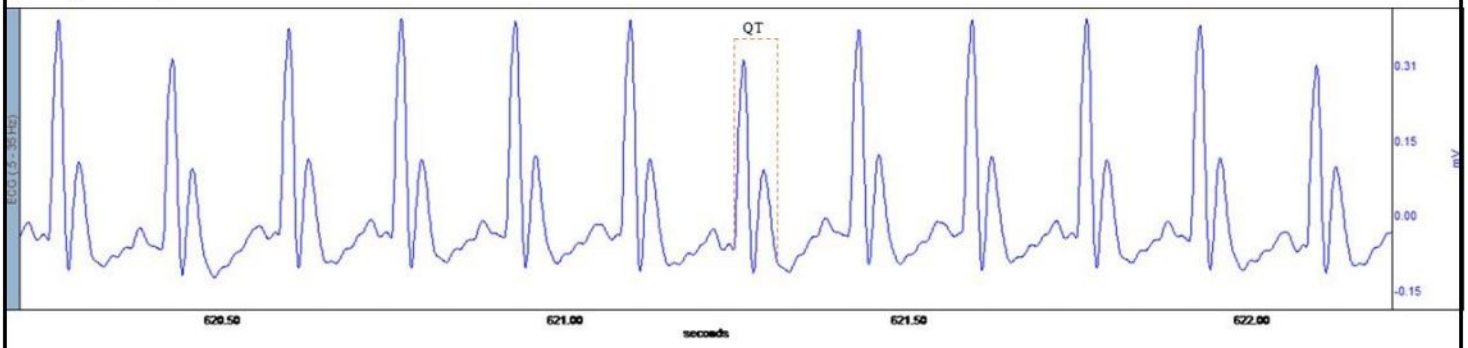


Group I , Day 7

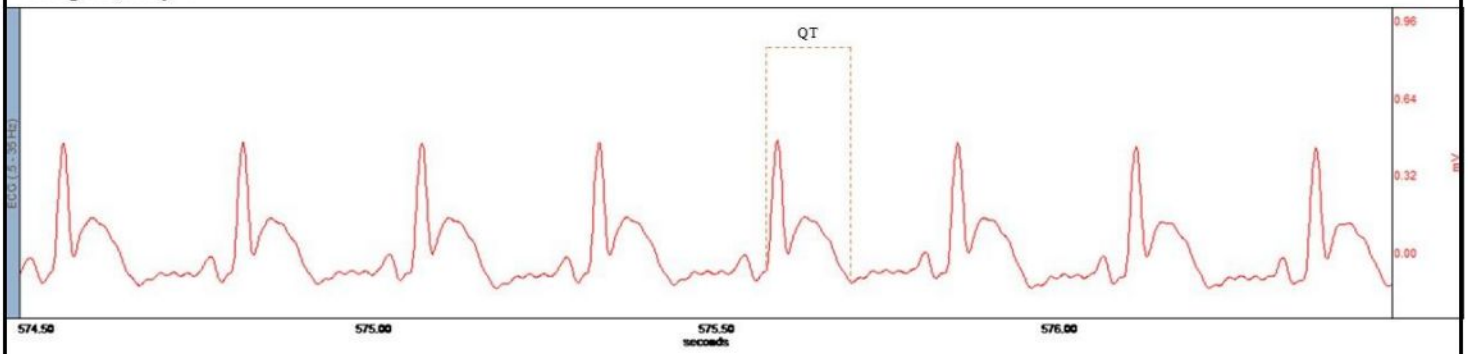


Group- I (FUR+ CLA)

Group II , Day 0

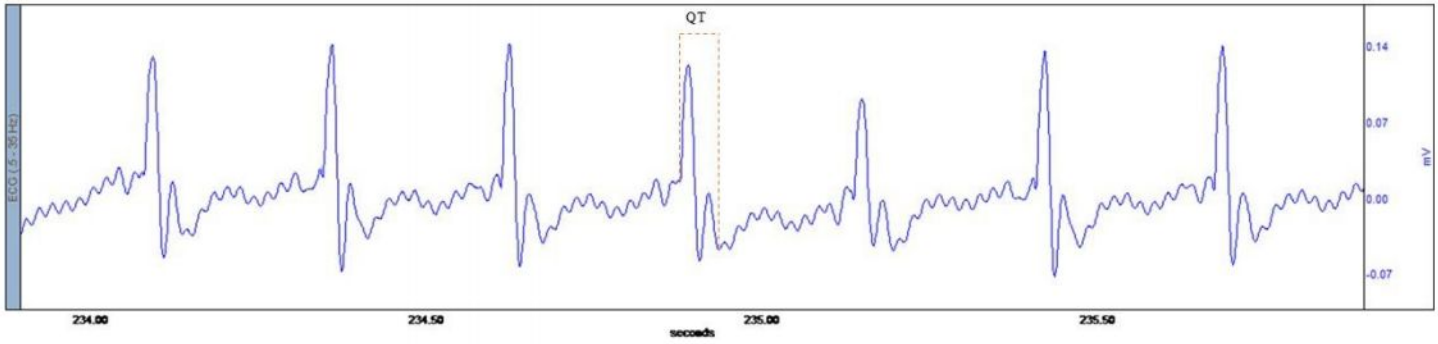


Group II , Day 7

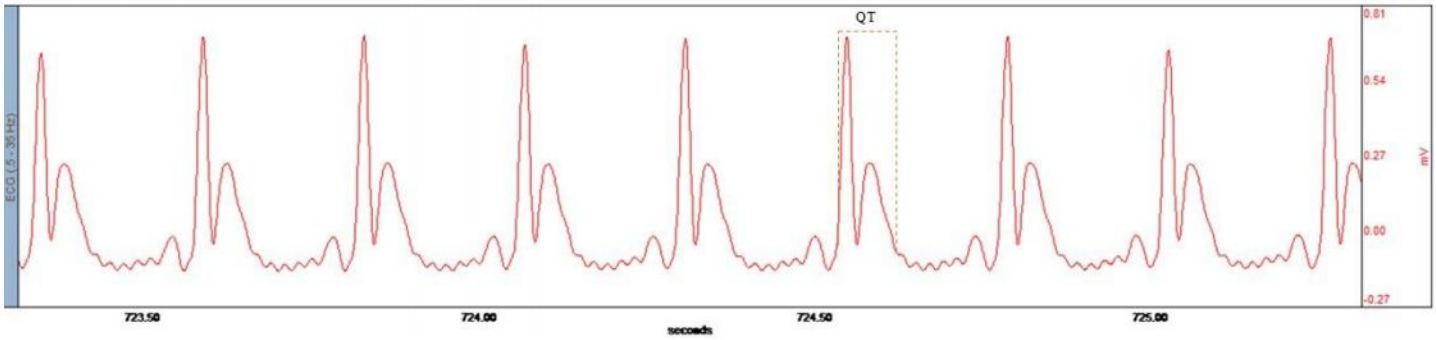


Group- II (FUR+ CLA+LTG-BD)

Group III , Day 0

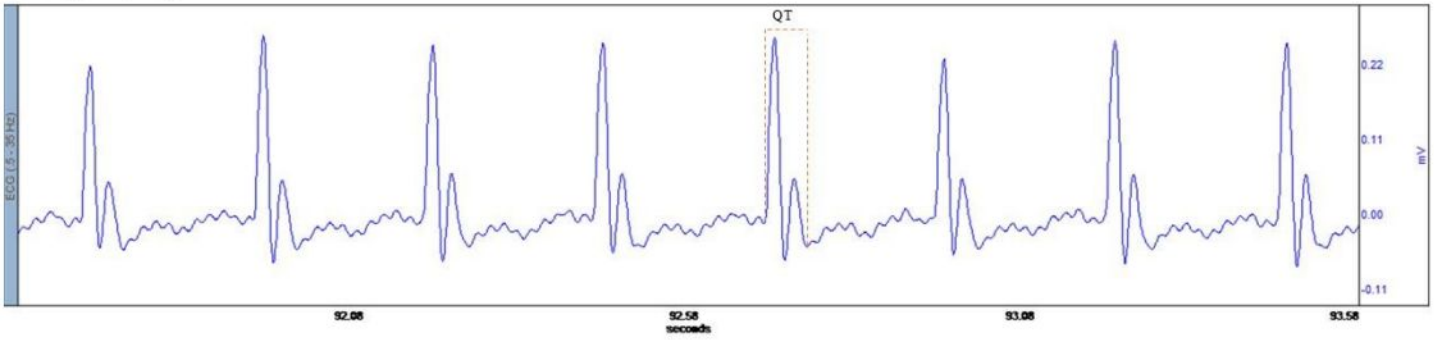


Group III , Day 7

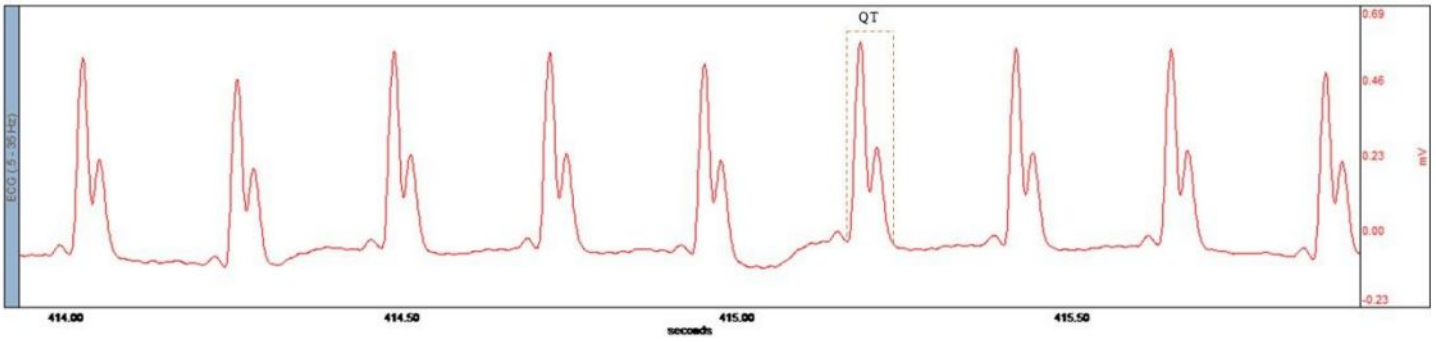


Group- III (FUR+ CLA+LTG-OD)

Group IV , Day 0



Group IV , Day 7



Group- IV (LTG ONLY)

7.1 Electrocardiograms Recording

Electrocardiograms (ECGs) were recorded from all animals in each group, facilitating the calculation of QTc values based on QT and R-R intervals. Given the inter-strain variability and the lack of established QT standards in rats, individual self-control values were employed as the normative reference. Significant increases in QTc values relative to self-control were deemed indicative of QT interval prolongation. Sample ECG tracings from each group, obtained on day seven of dosing, are presented in conjunction with their corresponding self-control recordings to enable comparative evaluation.

Table 6: ECG Data (Mean±SEM)

Electrocardiogram Data				
Groups		**QT (msec)**	**RR (msec)**	**QTc (msec)**
Group-I (FUR+CLA)	Self-Control	0.069±0.001	0.246±0.002	0.140±0.002
	7th Day	0.089±0.001	0.253±0.001	0.173±0.002
Group-II (FUR+CLA+LTG-BD)	Self-Control	0.066±0.001	0.255±0.003	0.122±0.001
	7th Day	0.139±0.001	0.244±0.004	0.287±0.002
Group-III (FUR+CLA+LTG-OD)	Self-Control	0.060±0.004	0.237±0.002	0.148±0.004
	7th Day	0.160±0.001	0.230±0.003	0.342±0.002
Group-IV (LTG)	Self-Control	0.072±0.002	0.196±0.001	0.183±0.005
	7th Day	0.100±0.001	0.191±0.001	0.271±0.002

7.1.1 Lamotrigine prolongs QT and QTc interval in hypokalaemic Rat only

After 7day treatment of four groups (Group1 to 4) with previously mentioned doses, the QT, RR and QTc data were taken and compared to the self-control data. In all three groups except Group IV, QT and QTc were significantly prolonged ($p<0.001$ at CL 95%) where RR interval was not shown any significant changed. This indicate that LTG has a potency to prolong QTc only in compromised groups.

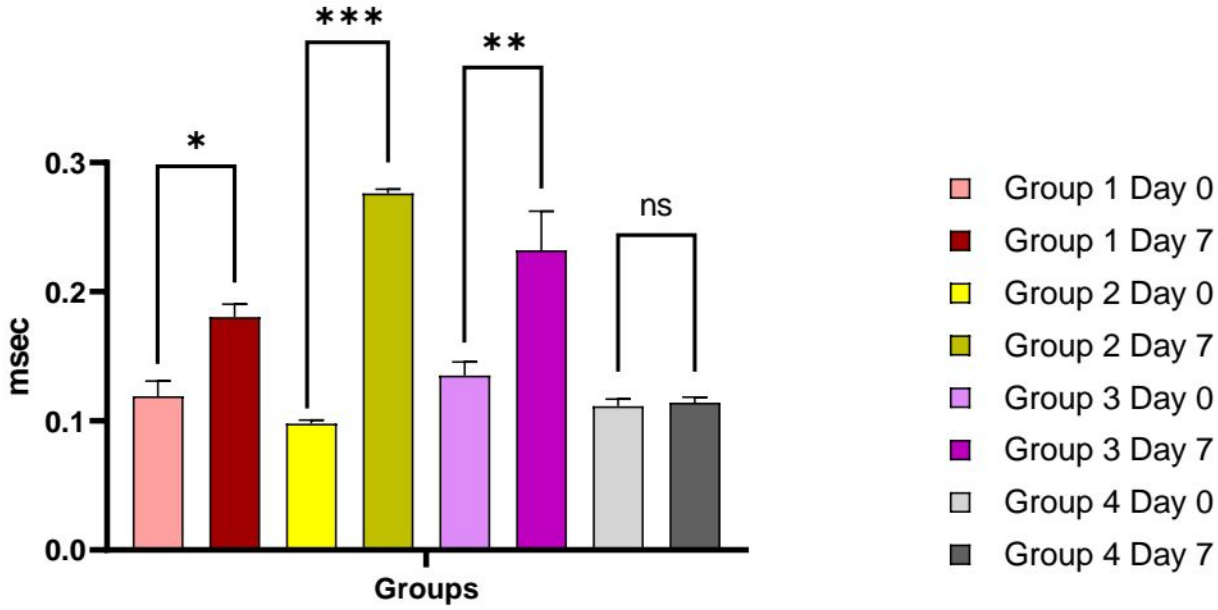


Fig-6 QTc interval of groups with respect to their corresponding self-control. Values expressed as Mean ± SD. ****p<0.001, n=6.

7.2 Serum electrolyte analysis

Table 7: Serum electrolyte Data (Mean±SEM)

Groups		MG^{2+} (meq/l)	K^{+} (meq/l)
Group-I (FUR+CLA)	Self-Control	2.198±0.176	5.020±0.007
	7th Day	1.536±0.255	4.110±0.051
Group-II (FUR+CLA+LTG-BD)	Self-Control	2.540±0.050	4.622±0.080
	7th Day	2.499±0.048	3.296±0.071
Group-III (FUR+CLA+LTG-OD)	Self-Control	1.676±0.296	3.975±0.072
	7th Day	1.861±0.084	2.223±0.000
Group-IV (LTG Only)	Self-Control	1.916±0.014	4.532±0.010
	7th Day	1.957±0.020	4.384±0.004

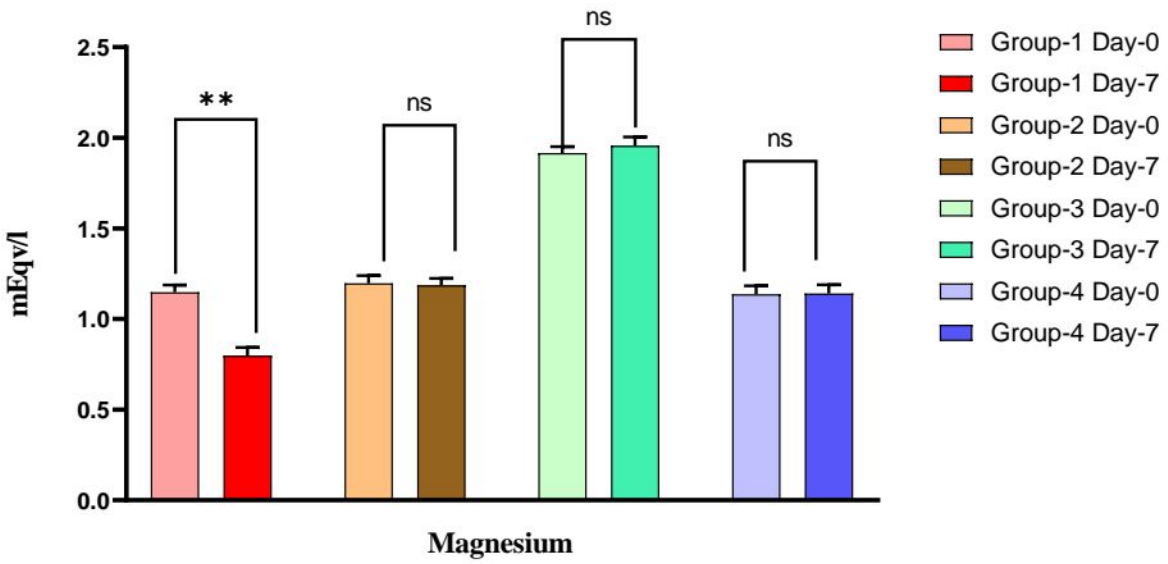


Fig 7-Serum magnesium level of groups with respect to their corresponding self-control. Values expressed as Mean ± SD. ****p<0.001, n=6.

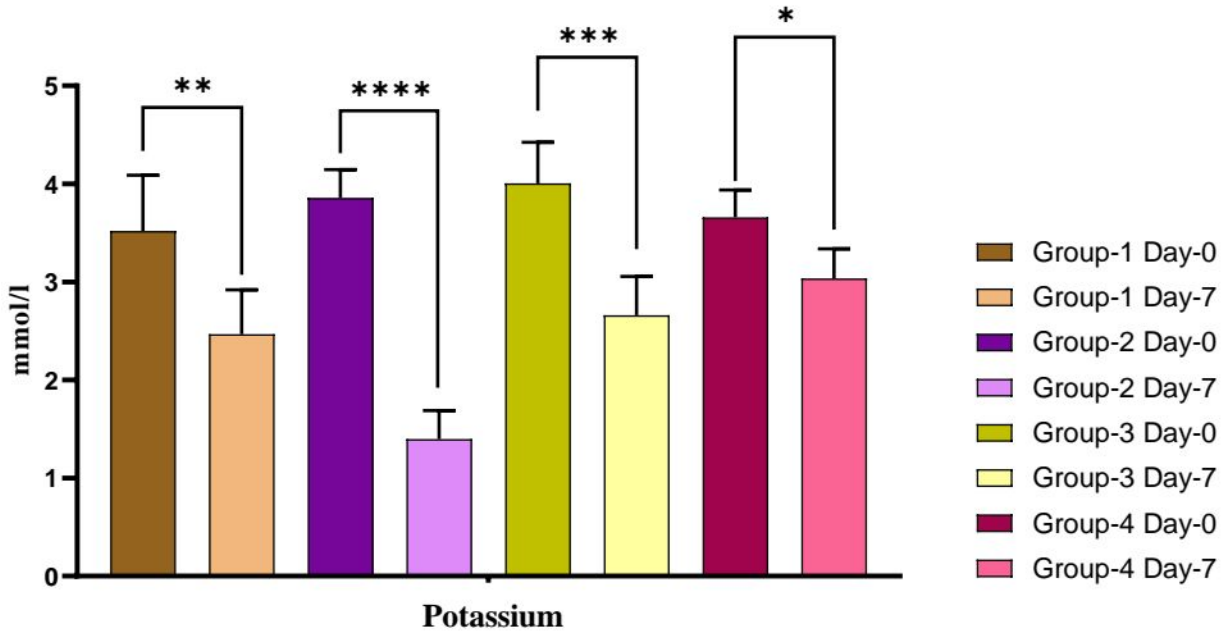


Fig 8-Serum Potassium level of groups with respect to their corresponding self-control. Values expressed as Mean ± SD. ****p<0.001, n=6

7.2.1 Lamotrigine creates hypokalemic condition in both provocative and non-provocative groups

The serum electrolyte data is presented in Table 7, while the grouped serum potassium and magnesium data of the experimental animals, along with their individual and group mean values, are illustrated in Figures 7 and 8. A comparative analysis of the seventh-day serum potassium data reveals a statistically significant decrease ($p < 0.001$, 95% confidence level) in Group I, Group II, Group III, and Group IV compared to their respective self-control values. Notably, the observed potassium levels fall below the established lower limits for blood potassium. In contrast, significant alterations in magnesium levels were detected in blood plasma. These findings collectively indicate the induction of hypokalemia, as evidenced by the comparison with respective self-control values.

CHAPTER - VIII

DISCUSSION

DISCUSSION

Lamotrigine (LTG; 3 dichlorphenyl-1,2,4-triazine) is a clinically useful antiepileptic drug, mainly administered as an add-on medication to other anticonvulsants in therapy resistant epilepsy (J. A. Messenheimer, 1995). It stabilizes neuronal membranes, reduces abnormal neuron firing, and prevents seizures by stabilizing the brain's electrical signal transmission selectively binding and inhibiting voltage-gated sodium channels in the brain. (T. Betchel et al., 2020), (Meldrum, 1994). It also blocks the Ia current in hippocampal neurons, causing a state-dependent blockade of the channel with higher affinity to the inactivated state, which is believed to interact with A-type potassium channels. (Huang et al., 2004). It has been found to affect cardiac sodium channels, may have prolonging effect the action potential in animals. (Huang et al., 2004), (Contreras Vite et al., 2022). In addition to this effects, LTG also inhibits the release of the excitatory neurotransmitters glutamate and aspartate. (Meldrum, 1994),(Choi & Morrell, 2003).

It will be relevant to mention that hypokalemia, characterized by low potassium levels, can lead to early after depolarizations in cardiac cells, triggering arrhythmias, as it inhibits the Na-K pump, which maintains sodium and potassium ion balance, resulting in increased intracellular sodium levels (Pezhouman et al., 2015) . This disrupts cardiac cell electrical activity, activating the Ca-calmodulin kinase II pathway and enhancing the late sodium current and L-type calcium current, leading to EAD generation. Hypokalemia inhibits outward potassium currents, such as the delayed rectifier potassium current (IK) and the transient outward current (Ito), which are responsible for repolarizing the cardiac cells during the action potential. (Osadchii, 2010)

The study involved 24 animals divided into four groups, each with six animals. The groups were divided into three groups: Compromised (intra-peritoneal administration of furosemide and clarithromycin), Compromised + Test drug OD (same injections with single oral daily dose of LTG), Compromised + Test drug BD (same injections with twice daily oral dose of LTG), and Only oral LTG. After a 7-day treatment period, blood was withdrawn from each group by trans-cardiac puncture under mild anesthesia, centrifuged at 4,000 rpm, and stored at -20^{0}c.

It was observed that all groups showed a prolongation of QTc value at day 7 as compared to day 0, except for Group IV. Group II and III showed more QTc prolongation than Group I or compromised group. Group II had more prolonged QTc than Group III. Plasma electrolyte

analysis showed significant changes in potassium concentration, indicating a low potassium level. Results of ECG and plasma electrolyte concentration assay indicates provocation for arrythmia in compromised groups in which concomitant induction of a diuratic (Furosemide) and a Ikr channel expression blocker (Clarithromycin) occurred along with test drug (LTG). LTG may induce this provocation by causing hypokalemia as a case report showed tendancy of hypokalemia in LTG overdosed individuals (Lofton & Klein-Schwartz, 2004). This leads to membrane hyperpolarization and increased excitation threshold. Due to this conduction is slowed down leading to decrease of excitation wavelength. Hypokalemia also leads to decrease in outward current movement through rectified potassium channels causing to prolonged repolarization. This leads to increased APD dispersion and early after depolarization. All this may be a potential cause of re-entrant arrhythmias.

Clarithromycin being inhibitor of translation Ikr channel; prevents the outflow of K+ current and LTG shows some additive effect. This may demonstrate that LTG may only have a proarrythmogenic effect where the drug can only provoke QT prolongation when it is associated with other arrythmogenic drug. A possible reason for aforementioned effect is repolarization reserve, in this phenomenon any adverse event is counterbalanced. Repolarization reserve provides a physiologic check to prevent excess action potential duration lengthening and QT prolongation. (Varró & Baczkó, 2011) . However, during conditions like Ikr channel inhibition, and severe compromisation of potassium level repolarization reserve fails to prevent QT lengthening. Thus, when combined with CLA and LTG, the repolarization reserve is diminished, but not in the group IV where only LTG doesn't have any significant effect on APD.

This analysis of the data suggests that LTG has proarrhythmic potential, manifesting as QT interval prolongation, when co-administered with arrhythmogenic substances. Nevertheless, additional studies are necessary to comprehensively understand the underlying mechanisms and to ascertain the clinical implications of this interaction.

CHAPTER IX

CONCLUSION

CONCLUSION

Although Torsade de Pointes remains one of the major causes of sudden cardiac death worldwide, hence needing continuous research and vigilance, even after enormous progress made in reducing mortality due to drug-induced QT prolongation, a number of factors have not been addressed in such cases. This presents a new framework that can significantly increase the sensitivity for the detection of QT prolongation and hence pick up subtle propensities, which otherwise may go undetected. What is more, the roles of potassium and newly discovered pathways that prolong action potential duration must be considered in the future screening of drugs for QT prolongation. Our results indicate that even such commonly used drugs as LTG can provoke arrhythmias and QT interval prolongation when co-administered with other drugs known to prolong QT or in patients with predisposed LQT syndromes. This physiological phenomenon is pertinent to a key issue of actual clinical practice: the potential for enhancing cardiac risks arising from drug-, herb-, or food-induced hypokalemia, particularly in the presence of medications such as LTG—as was attested by QT interval measures in this case. A much more aggressive screening method must hence be adopted that takes into consideration repolarization reserve considerations and makes use of contemporary concepts of personalized medicine, for instance, genome-wide patient analysis, with the view of introducing higher levels of safety into drug use. The other urgent area for research at this point is the development of risk assessment models, which would include various factors in the prediction and prevention of Torsade de Pointes. Studies in the future have to look into the molecular mechanisms of QT prolongation and new therapeutic approaches aimed at reducing this risk. Ultimately, it will require a multidisciplinary approach to advances in systems biology, pharmacology, and personalized medicine in developing comprehensive drug screening methodology that will bring safety to patients.

CHAPTER X

REFERENCES

REFERENCES

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