WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 14, Issue 13, 414-429. Review Article ISSN 2277–7105

WHEN DRUGS TURN DEADLY: UNDERSTANDING TORSADES DE POINTES

Dr. Madhanraj N.[1*] and Mr. Jeba Ruban F.[2]

[*1]Department of Pharmacy Practice, Karpagam College of Pharmacy, Coimbatore, India.

[2]Department of Cardiology, Dhanalakshmi Srinivasan Medical College and Hospital, Preambular, India.

Article Received on
08 May 2025

Revised on 28 May 2025
Accepted on 18 June 2025

DOI: 10.20959/wjpr202513-37362

***Corresponding Author**
Dr. Madhanraj N.
Department of Pharmacy Practice, Karpagam College of Pharmacy, Coimbatore, India.

ABSTRACT

This article explores drug-induced Torsades de Pointes (TdP), a severe cardiac arrhythmia. It details cases involving intravenous amiodarone, where 1.5% of patients developed TdP, recovering without mortality. Extreme eperisone overdose and polypharmacy in elderly patients significantly elevate TdP risk due to QT prolongation and drug interactions. Other causative agents include clarithromycin, ondansetron, levetiracetam, loperamide, and moxifloxacin, often exacerbated by electrolyte imbalances. Women exhibit higher susceptibility to drug-induced TdP. Additionally, cannabinoid use and antipsychotic polypharmacy are identified risks. The article underscores the critical need for vigilance in prescribing and monitoring to prevent this life-threatening condition.

KEYWORD: Torsades de Pointes (TdP), QT Prolongation, Drug-Induced Arrhythmias, Cardiac Toxicity.

INTRODUCTION

Drug-induced Torsades de Pointes (TdP) is a polymorphic ventricular tachycardia characterized by a twisting of the QRS complexes around the isoelectric baseline on an electrocardiogram (ECG).[1,2] This potentially fatal arrhythmia is a significant concern in clinical practice due to its association with sudden cardiac death.[3] TdP typically occurs in the setting of a prolonged QT interval, which can be congenital or acquired. While congenital long QT syndrome is a genetic disorder, acquired QT prolongation is more commonly encountered and is frequently precipitated by medications.[4,5]

The underlying mechanism of drug-induced TdP involves the blockade of the rapid component of the delayed rectifier potassium current (IKr), encoded by the *hERG* gene (human Ether-à-go-go-Related Gene). This blockade leads to a delay in repolarization of ventricular cardiomyocytes, thereby lengthening the action potential duration and the QT interval.[6,7] A wide array of commonly prescribed drugs across various therapeutic classes have been implicated in QT prolongation and TdP, including antiarrhythmics, antibiotics, antipsychotics, antidepressants, and antihistamines.[8,9,10]

The risk of drug-induced TdP is multifactorial, depending on the specific drug, its dosage, drug-drug interactions, and patient-specific factors.[11] Genetic predispositions, electrolyte imbalances (e.g., hypokalemia, hypomagnesemia), underlying cardiac conditions, and female gender are recognized risk factors that can augment susceptibility to drug-induced TdP.[12,13,14,15] Early identification of at-risk patients and careful medication management, including thorough history taking, ECG monitoring, and awareness of drug-drug interactions, are paramount in preventing this life-threatening arrhythmia.[16,17,18] Despite extensive research, drug-induced TdP remains a challenging clinical problem requiring a comprehensive understanding of its pathophysiology and risk factors for effective prevention and management.[19,24,27,28]

MATERIALS AND METHODOLOGY

Research into drug-induced Torsades de Pointes (TdP) employs diverse methodologies, ranging from retrospective case series and reviews to controlled animal studies and clinical trials, to understand incidence, mechanisms, and risk factors. The following outlines key methodological approaches identified from various studies.

I. Study Design and Patient Populations

- **Retrospective Case Series/Reviews:** Many studies rely on retrospective analysis of patient medical records or pharmacovigilance databases. For instance, the incidence of IV amiodarone-induced TdP was determined by reviewing 268 patient records from January 2014 to August 2016[5] Similarly, polymedicated elderly patients presenting with TdP were analyzed as consecutive cases[10] Reviews of published literature examine existing case reports and clinical data for drugs like moxifloxacin[3] or clarithromycin.[7]

- **Case Reports:** Individual case reports detail unique presentations of drug-induced TdP, providing in-depth clinical trajectories. Examples include TdP induced by extreme

eperisone overdose in a 46-year-old woman[19], a single oral dose of ondansetron in a 60-year-old woman,[26] levetiracetam in a 59-year-old male,[4] loperamide overdose in a 27-year-old female,[28] and concomitant chlorpheniramine and propranolol use in a 35-year-old man.[14]

- **Animal Models:** Preclinical studies utilize animal models to investigate mechanisms and risk factors. A canine model of acquired Long QT Syndrome type 1 (LQT1) was used to study seizure-induced TdP. Dogs were pre-treated with JNJ 282 (IKs blocker) to induce QT prolongation, followed by pentylenetetrazol (PTZ) administration to induce seizures, with simultaneous EEG and ECG monitoring.[1] Sex-related differences were explored using male and female human induced pluripotent stem cell cardiomyocytes (hiPSC-CMs).[6]

- **Observational Studies/Database Analysis:** Large-scale data from adverse event reporting systems (e.g., US FDA AERS, EMA Eudra Vigilance, WHO VigiBase) are analyzed to estimate the frequency of TdP associated with specific drugs like moxifloxacin.[3] Population-based studies, such as those in Taiwan, assess the risk of serious arrhythmia with fluoroquinolones.[3]

II. Interventions and Measurements

- **Drug Administration**
  - **Clinical:** Amiodarone was administered intravenously at 1 gm/day.[5] Eperisone overdose involved self-ingestion of 15.3g.[19] Ondansetron was a single 4 mg oral dose.[26] Levetiracetam was administered intravenously (1000 mg) and later orally.[4] Loperamide was ingested at supratherapeutic doses.[28] Chlorpheniramine (4 mg) and propranolol (20 mg) were used concomitantly.[14]

  - **Preclinical:** JNJ 282 (0.5 mg/kg orally) was given to dogs to induce LQT1, and PTZ (1.5 mg/kg/min i.v.) was infused to induce seizures.[1]

Drug-Induced Torsades De Pointes with Intravenous Amiodarone

The study investigated the incidence, presentation, and outcomes of drug-induced Torsades de Pointes (TdP) with intravenous (IV) amiodarone. From January 2014 to August 2016, 268 patients received IV amiodarone for various conditions including ventricular tachycardia and atrial arrhythmias. A uniform dosing of amiodarone, targeting 1 gm/day, was used.

Out of the 268 patients, 4 (1.5%) developed pause-dependent TdP that degenerated into ventricular fibrillation. These patients, predominantly female (1:3 M:F ratio), had a mean age of 51.25±9.17 years. TdP occurred after a mean amiodarone dose of 690±176.63 mg, infused over 12±5.88 hours. The QTc interval at the time of TdP was 505±9.02 ms, which normalized to 433.75±6.13 ms within 48-72 hours of amiodarone cessation. Notably, there was no immediate or late mortality, and all patients were well at 5-10 months of follow-up. None of the patients tested positive for common Long QT Syndrome genes.[5]

Torsade De Pointes Induced by Extreme Eperisone Overdose a Case Report

In a separate case, a 46-year-old woman presented to the Emergency Center with QTc prolongation (660 msec) and Torsades de Pointes following an extreme overdose of eperisone, a centrally acting antispasmodic agent. She reportedly ingested 306 tablets, totaling 15.3g of eperisone. Although the arrhythmia initially resolved with electric defibrillation, non-sustained ventricular tachycardia frequently recurred. Electrolyte levels (serum potassium, calcium, and magnesium) were within normal ranges. The ventricular arrhythmias became sporadic after intravenous amiodarone administration and completely disappeared 4 hours after admission. Her QTc interval decreased to 487 msec 32 hours post-admission and eventually normalized, leading to discharge on day 2. Serum analysis revealed an eperisone concentration of 6387 ng/ml on arrival, approximately 1000 times higher than the therapeutic concentration, indicating that eperisone overdose can induce significant QTc prolongation and TdP.[19]

Drug Induced Torsades De Pointes in Elderly Polymedicated Patients

Polymedication, affecting one in three patients over 65 years old, carries a significant risk of adverse drug events, particularly malignant ventricular arrhythmias like Torsades de Pointes (TdP) due to drug interactions that prolong the QT interval. This complication is potentially lethal, necessitating careful recognition of causative drugs and close monitoring when co-administration is unavoidable.

Three consecutive cases of elderly polymedicated female patients (aged 84, 85, and 74) presenting with drug-induced polymorphic ventricular tachycardia due to prolonged QT interval were reported. All patients were receiving multiple chronic medications, including drugs known to prolong the QT interval such as amiodarone, escitalopram, and sulpiride. Electrolyte disturbances, including hypokalemia, hypomagnesemia, and hypocalcemia, were also identified as contributing factors.

In each case, withdrawal of the offending QT-prolonging drugs, correction of electrolyte imbalances, and in some instances, temporary ventricular pacing led to the resolution of TdP and normalization of the QT interval. These cases highlight the heightened vulnerability of elderly, polymedicated patients to drug-induced TdP, underscoring the importance of vigilant medication review and management to prevent this life-threatening arrhythmia.[10]

Clarithromycin-Induced Torsades De Pointes

Clarithromycin, a macrolide antibiotic commonly used for respiratory infections and *Helicobacter pylori* eradication, has been increasingly reported to cause QT prolongation and Torsades de Pointes (TdP). This rare but potentially fatal ventricular arrhythmia is associated with the drug's blockade of the potassium channel (Ikr), leading to a prolonged QT interval. A case study highlights this risk: a 63-year-old woman with a history of coronary artery disease, *H. pylori* gastritis, and hypertension presented with weakness, nausea, and vomiting. She was on a clarithromycin-based regimen for *H. pylori* eradication. Upon admission, her corrected QT (QTc) interval was significantly prolonged at 597 milliseconds, compared to a baseline of 465 milliseconds. She also presented with hypokalemia (2.3 mEq/L) and hypomagnesemia (1.5 mg/dL), both within normal ranges previously but contributing to increased risk.

Hours after admission, she developed pulseless polymorphic ventricular tachycardia, requiring defibrillation and chest compressions. After electrolyte replacement and withdrawal of clarithromycin, her QTc normalized to 468 milliseconds. She was discharged three days later on an alternative *H. pylori* regimen without macrolides. This case underscores the importance for clinicians to be aware of the potential for clarithromycin-induced TdP, especially in patients with existing cardiac risks or electrolyte imbalances.[02]

Ondansetron Induced Torsades De Pointes A Case Report

A single oral dose of Ondansetron, an antiemetic, can precipitate Torsades de Pointes (TdP) and other arrhythmias, particularly in patients with risk factors that may prolong the QTc interval.

A case report describes a 60-year-old woman with a history of gastritis and sinus bradycardia with first-degree atrioventricular block, who presented with nausea and vomiting. Her ECG showed sinus bradycardia (37 bpm), first-degree AV block, and a QTc of 408 ms. She was treated with 4 mg of oral Ondansetron. Two hours later, telemetry revealed sinus bradycardia

(37-45 bpm) with episodes of ventricular tachycardia, progressing to polymorphic ventricular tachycardia with beat-to-beat variations characteristic of TdP.

Urgent treatment with 2g intravenous magnesium sulfate and 400 mg oral magnesium oxide successfully terminated the arrhythmia. This case emphasizes that even a single dose of Ondansetron can trigger TdP in susceptible individuals. Risk factors for TdP, such as cardiac diseases, congenital long QT syndrome, female gender, bradycardia, hypothermia, hypomagnesemia, hypokalemia, and concomitant medications that prolong the QT interval, should be carefully considered before administering Ondansetron.[26]

Table 1: Drugs that triggered torsade de pointes.[07]

Antibiotics	Psychotropic agents	Antiarrhythmic agents	Others
Erythromycin (*n* = 4)	Donepezil (*n* = 5)	Sotalol (*n* = 7)	Terodiline (*n* = 6)
Levofloxacin (*n* = 4)	Citalopram (*n* = 4)	Amiodarone (*n* =5)	Astemisol (*n* = 2)
Gatifloxacin (*n* = 2)	Haloperidol (*n* = 2)	Quinidine (*n* = 3)	Cisapride (*n* = 1)
Garenoxacin (*n* = 2)	Risperidone (*n* =2)	Dofetilide (*n* = 2)	Ranolazine (*n* =1)
Roxithromycin (*n* =2)	Maprotiline (*n* =1)	Ibutilide (*n* = 1)	Terfanidine (*n* =1)
Moxifloxacin (*n* = 2)	Fluoxetine (*n* = 1)	Pilsicainide (*n* = 1)	Ketanserin (*n* = 1)
Azithromycin (*n* = 1)	Paroxetine (*n* = 1)	–	–
Clarithromycin (*n* =1)	–	–	–

Levetiracetam-Induced Torsades De Pointes

Levetiracetam, a widely used anti-epileptic medication known for its favorable safety profile, has rarely been associated with Torsades de Pointes (TdP) and cardiac arrest. A unique case describes a 59-year-old male who developed TdP and cardiac arrest following levetiracetam administration, representing only the second reported case of levetiracetam-induced TdP and the first documenting associated cardiac arrest.

The patient, with a history of a seizure disorder, received intravenous levetiracetam (1000 mg) and lorazepam. Post-administration, his ECG showed a significantly prolonged QTc interval of 646 milliseconds. Concurrently, he developed hypokalemia (2.9 mmol/L) and hypomagnesemia (1.3 mg/dL). He subsequently experienced TdP on telemetry, which rapidly degenerated into ventricular fibrillation and cardiac arrest.

Immediate defibrillation restored spontaneous circulation and sinus rhythm. Despite initial potassium and magnesium supplementation, electrolyte levels remained low, and the QTc interval remained prolonged. Upon switching to Divalproex, his potassium and magnesium levels normalized, and the QTc interval returned to 456 milliseconds. This case underscores

the critical importance of recognizing levetiracetam as a potential, albeit rare, cause of QT prolongation and TdP, particularly in the presence of electrolyte imbalances.[04]

Loperamide-Induced Torsades De Pointes

Loperamide, a readily available over-the-counter antidiarrheal, has emerged as a drug of abuse due to its opioid receptor activity at supratherapeutic doses. This misuse can lead to severe cardiac toxicity, including prolonged QTc, wide QRS rhythms, severe bradycardia, polymorphic ventricular tachycardia (PVT), and cardiac arrest.

A case report details a 27-year-old female with a history of heroin abuse who suffered Torsades de Pointes (TdP) resulting in cardiac arrest due to loperamide overdose. She was found in an altered mental state with agonal breathing and a bottle of loperamide pills nearby. Despite initial naloxone administration and intubation efforts by EMS, she remained distressed. Upon arrival at the ED, her ECG showed a QTc interval of 594 ms. She subsequently developed persistent PVT/TdP, requiring four minutes of CPR and defibrillation.

Further management involved aggressive magnesium repletion, isoproterenol, and lidocaine. Although her QTc improved to 405 ms after 24 hours, she continued to experience arrhythmias. Following evaluation by an electrophysiologist, she was started on mexiletine, and other medications were tapered. Her QTc eventually normalized, and she was discharged with a plan for outpatient follow-up. This case highlights the dangerous cardiac effects of loperamide overdose, underscoring the need for increased awareness among healthcare professionals regarding its potential for misuse and toxicity.[28]

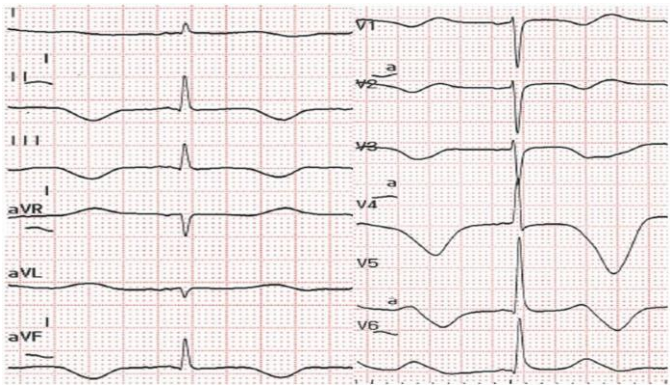

Figure: 1 A 12-lead electrocardiogram showing different T wave morphologies over.

Individual leads in the same patient[24]

Drug-Induced QT Prolongation and Its Implications for Anticancer Therapy

Drug-induced QT prolongation, a global index of ventricular repolarization, can lead to Torsades de Pointes (TdP), a polymorphic ventricular tachycardia that may cause syncope or sudden cardiac death. While many drugs have a small effect on QT, marked prolongation is a serious concern. The primary mechanism involves blocking the IKr potassium current, predominantly mediated by the *hERG* gene.

Recent research, particularly concerning anticancer drugs, reveals new pathways for QT prolongation beyond IKr blockade. For example, some tyrosine kinase inhibitors can prolong cardiac action potentials, and this effect can be mitigated by intracellular phosphatidylinositol 3,4,5-trisphosphate. This suggests that inhibition of enzymes like phosphoinositide 3-kinase (PI3K) or upstream kinases, as well as enhanced inward "late" sodium current, can contribute to QT prolongation.

Understanding these non-IKr-dependent mechanisms is crucial for assessing the risk of TdP, not only with anticancer therapies but also with other QT-prolonging drugs. This expanded knowledge allows.

Inhibition of CYP3A4		**Inhibition of CYP2D6**	
Inhibitors	**Substrates**	**Inhibitors**	**Substrates**
Antifungals • Itraconazole • Ketoconazole • Posaconazole • Voriconazole	Amiodarone Disopyramide Dofetilide Pimozide	**Neuropsychiatrics** • Bupropion • Duloxetine • Fluoxetine • Paroxetine	Flecainide Quinidine Thioridazine
Macrolides Erythromycin Clarithromycin		**Antifungal** • Terbinafine	

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Table 2: Common Pharmacokinetic Drug Interactions Associated With Torsades de Pointes.

Azithromycin			
Protease Inhibitors Atazanavir Darunavir/ritonavir Fosamprenavir Indinavir Nelfinavir			

Saquinavir Tipranavir			
CYP = cytochrome P450			

Understanding of How Intracellular Signaling Systems Modulate QT and Associated Arrhythmia Risk, Which is Vital for Safe Drug Development and Patient Management, Especially in Oncology Where QT-Prolonging Agents are Increasingly Used.[16]

Sex-Related Differences in Drug-Induced Torsades De Pointes

Clinical studies indicate that women have a two-fold greater risk of developing drug-induced QT prolongation and Torsades de Pointes (TdP) compared to men. This heightened susceptibility cannot be fully explained by differences in drug plasma levels alone; rather, it suggests a greater intrinsic sensitivity in women. Significant sex differences are observed in human cardiac electrical activity, with women exhibiting a longer rate-corrected QT (QTc) interval and steeper QT-to-RR ratio slopes than men. These differences become apparent after puberty, as the QTc interval shortens in men but not in women, coinciding with an increased risk of drug-induced cardiac events in women.

The underlying molecular mechanisms involve genetic and hormonal influences. Female-derived human induced pluripotent stem cell cardiomyocytes (hiPSC-CMs) have shown greater sensitivity to IKr blocker-induced field potential duration (FPD) prolongation and arrhythmias compared to male-derived hiPSC-CMs. This is partially attributed to reduced repolarization reserve and differential expression of cardiac ion channel genes, such as *KCNE1*, which is expressed at higher levels in males and contributes to IKs function, an important repolarization reserve current. While sex hormones like estradiol can prolong QTc and dihydrotestosterone can shorten it, their direct effects on hiPSC-CMs' sensitivity to IKr blockers were limited in this study, suggesting that fundamental genetic/genomic differences play a more significant role in determining sex differences in drug-induced QT prolongation and TdP.[06]

Torsades De Pointes Induced by Cannabinoid Use

The increasing use of tetrahydrocannabinol (THC) and related cannabinoid products for recreational and medicinal purposes has been linked to a rise in complications, including cardiac arrhythmias such as Torsades de Pointes (TdP). This highlights a growing concern about the arrhythmogenic properties of these substances.

A case report describes a 66-year-old female with a history of recreational cannabinoid and tobacco use who presented with syncope and was later found to have polymorphic ventricular tachycardia. Her initial EKG revealed a significantly prolonged QTc interval of 517 ms, despite normal electrolyte levels. An extensive cardiac workup, including catheterization, yielded no alternative cause for the arrhythmia.

Upon inpatient telemetry, she developed an episode of polymorphic ventricular tachycardia lasting approximately 5 seconds, coinciding with another syncopal event. The patient reported occasional recreational cannabinoid gummy use prior to hospitalization. She was advised to abstain from cannabinoid products and was started on nadolol 10 mg daily, which led to the normalization of her QTc interval. Her QTc remained prolonged throughout her 10-day hospitalization but normalized at a 6-week outpatient follow-up. This case underscores the importance of considering cannabinoid use in patients presenting with syncope of unknown etiology and recognizing its potential to induce TdP.[13]

Moxifloxacin Induced Torsades de Pointes

Moxifloxacin, a widely used fluoroquinolone antibacterial, has been associated with QT interval prolongation (QTIP) and Torsades de Pointes (TdP), despite its favorable pharmacological profile. While it generally causes mild to moderate QTIP in healthy individuals (11.5-19.5 ms), marked QTIP (>60 ms) and TdP have been reported in high-risk patients.

According to global pharmacovigilance centers, numerous cases of moxifloxacin-related TdP have been reported. For instance, the US FDA AERS database recorded 147 cases of TdP, with 16 fatalities. Similarly, the EMA EudraVigilance received 109 TdP cases (4 fatal), and the WHO VigiBase reported 154 TdP cases.

The mechanism involves moxifloxacin binding to the Tyr652 residue in the S6 pore domain of the hERG potassium channel, affecting ventricular repolarization. Risk factors such as hypokalemia, concomitant administration of other QT-prolonging drugs, prolonged baseline QT interval, and genetic predisposition can exacerbate moxifloxacin-induced QTIP. Therefore, thorough patient assessment and identification of high-risk individuals are crucial before prescribing moxifloxacin. In cases where its use is inevitable, close ECG monitoring is recommended to prevent life-threatening cardiac events.[03]

The Risk for Torsades De Pointes

Patients with schizophrenia face a 2.5- to 3-fold increased standardized mortality rate, largely due to Sudden Cardiac Death (SCD) caused by cardiac arrhythmias like Torsades de Pointes (TdP). This arrhythmia is linked to prolonged cardiac repolarization, reflected by a prolonged QTc interval and T wave abnormalities on an electrocardiogram (ECG).

Between 6% and 12% of patients taking antipsychotic drugs exhibit a prolonged QTc interval. The risk is compounded by antipsychotic polypharmacy and the co-prescription of non-antipsychotic psychotropics (NAPs) like mood stabilizers and antidepressants, which also contribute to QTc prolongation.

A study assessing cardiac arrhythmia risk in 169 hospitalized schizophrenia patients found that nearly 25% were at risk when considering both QTc duration and T wave abnormalities. Key risk factors for TdP in this population include gender, age, hepatic dysfunction, and electrolyte disturbances. The study highlights the need for abundant caution when prescribing polypharmacy in this vulnerable patient group, emphasizing that a balance between risks and benefits must be carefully considered given the potential for serious cardiac adverse events.[11]

Torsades De Pointes Induced by Concomitant Use of Chlorpheniramine and Propranolol

Drug-induced Torsades de Pointes (TdP) is a rare yet potentially fatal adverse effect of various medications. While typically associated with QT prolongation, TdP can, unusually, occur without it. This case report highlights such an instance involving the concomitant use of chlorpheniramine and propranolol.

A 35-year-old man was hospitalized with acute chest pain, palpitation, and syncope. He had been prescribed chlorpheniramine (4 mg) for an upper respiratory infection and was also taking propranolol (20 mg) daily for essential tremor and anxiety. His symptoms, including altered consciousness and irregular pulse, appeared one hour after taking both medications together.

Despite the patient's ECG showing no QT prolongation, he experienced an attack of polymorphic ventricular tachycardia that degenerated into ventricular fibrillation, requiring immediate defibrillation. His electrolytes were normal, and cardiac angiography revealed no coronary artery disease. The authors concluded that the TdP was likely triggered by the

synergistic hERG channel blockade of chlorpheniramine and propranolol, emphasizing that TdP can occur even in the absence of a prolonged QT interval, necessitating vigilance with commonly used medications.[14]

Seizure-Induced Torsades de Pointes

Epilepsy patients face a heightened risk of sudden death, often attributed to Sudden Unexpected Death in Epilepsy (SUDEP), a phenomenon whose mechanisms are not fully understood. Cardiac arrhythmias are a suspected contributor to SUDEP. This study investigated the link between seizures and Torsades de Pointes (TdP) using a canine model of acquired Long QT Syndrome type 1 (LQT1).

Dogs were pre-treated with JNJ 282, a selective IKs blocker, to induce a pronounced QT prolongation, mimicking LQT1 syndrome. Subsequently, the proconvulsive compound pentylenetetrazol (PTZ) was administered to induce seizures. Simultaneous electroencephalographic (EEG) and electrocardiogram (ECG) measurements were conducted. The results showed that while PTZ induced spiking on the EEG and seizures in all treated dogs, TdP-like cardiac arrhythmias (specifically R-on-T phenomena and salvos leading to TdP/ventricular fibrillation) were observed exclusively in the LQT1 group, where repolarization was already compromised. This suggests that a proconvulsive drug can trigger TdP in the presence of compromised cardiac repolarization (IKs blockade). This observation supports the hypothesis that prolonged QT intervals, whether genetic or drug-induced, could be a significant risk factor for SUDEP in epileptic patients.[01]

DISCUSSION

Drug-induced Torsades de Pointes (TdP) remains a critical clinical challenge, primarily driven by QT interval prolongation, often resulting from the blockade of the *hERG* potassium channel.[3,16] However, the pathophysiology is complex, involving diverse mechanisms and patient-specific susceptibilities.[6,16]

Individual medications carry varying risks. Intravenous amiodarone, for example, induced TdP in 1.5% of patients in one study, particularly in females with prolonged QTc.[5] Extreme overdoses, such as with eperisone, can cause significant QTc prolongation and TdP.[19]

Similarly, clarithromycin has been implicated, especially in patients with pre-existing cardiac risks or electrolyte imbalances.[7] Even a single dose of ondansetron can precipitate TdP in

susceptible individuals with risk factors.[26] Rare but severe cases include levetiracetam-induced TdP, often compounded by electrolyte disturbances.[4] and cardiotoxicity from supratherapeutic loperamide doses, leading to TdP and cardiac arrest.[28]

Polymedication in elderly patients significantly heightens TdP risk due to drug-drug interactions and common electrolyte imbalances.[10] Emerging evidence also highlights less obvious triggers, such as cannabinoid use.[13] and the concomitant use of drugs like chlorpheniramine and propranolol, which can induce TdP even without overt QT prolongation.[14] Moreover, non-IKr pathways, such as those affected by anticancer drugs targeting PI3K signaling, are increasingly recognized contributors to QT prolongation and TdP.[16] Sex differences also play a role, with women showing increased susceptibility.[6]

The broad range of implicated drugs and multifaceted risk factors underscore the necessity for meticulous patient assessment, continuous ECG monitoring, and vigilant medication management to mitigate the potentially fatal consequences of drug-induced TdP.[3,16]

CONCLUSION

In conclusion, drug-induced Torsades de Pointes (TdP) is a severe yet preventable adverse drug reaction arising from various mechanisms, predominantly QT prolongation through hERG channel blockade, but also involving complex non-IKr pathways and multifactorial patient susceptibilities.[3,16] The diverse range of medications capable of inducing TdP, from commonly used antibiotics like clarithromycin.[7] and moxifloxacin,[3] to antiemetics like ondansetron,[26] and even illicit substances such as cannabinoids.[13] necessitates a high index of suspicion in clinical practice.

Patient-specific factors, including age, gender, polypharmacy, and electrolyte imbalances, significantly modulate the risk of TdP.[6,10] The often unpredictable nature of TdP, sometimes occurring without overt QT prolongation, as seen with chlorpheniramine and propranolol co-administration.[14] underscores the need for comprehensive patient evaluation beyond standard ECG monitoring. Vigilant medication reconciliation, thorough risk assessment, and prompt correction of modifiable risk factors are paramount. Continued research into the precise mechanisms and predictive biomarkers of drug-induced TdP will further enhance patient safety and guide the development of safer pharmacotherapies.[16] Ultimately, a multidisciplinary approach involving clinicians, pharmacists, and researchers is essential to minimize the incidence of this life-threatening arrhythmia.

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