QT-PROLONGATION ASSOCIATED WITH MEDICATION COMBINATION IN HOSPITALIZED PATIENTS AT JOHNS HOPKINS ARAMCO HEALTHCARE (JHAH), KSA

ABSTRACT

Background: Long QT syndrome (LQTS) is a myocardial repolarization dysfunction characterized by QT-interval prolongation on electrocardiogram (ECG). Patients with long QT syndrome have a corrected QT interval (QTc) prolongation greater than 460 milliseconds (0.46 seconds). Normal corrected QT interval is <440 ms in both genders, whereas borderline QTc is 440-450 ms in men, and 440-460 ms in women. A QTc being equal to or more than 500 ms is considered clinically significant in both men and women. The long QT syndrome has a direct association with an increased risk of a serious type of arrhythmias called 'Torsades de Pointes (TdP)', a polymorphic ventricular tachycardia. This syndrome can be either drug-induced (acquired) or congenital. The current literature suggests that conditions like hypomagnesaemia or hypokalemia could significantly aggravate the acquired QTc prolongation.[5] In addition, various drug classes are considered major contributors in developing long QT syndrome. Antiarrhythmic drugs, antipsychotics, calcium channel blockers, antihistamine, antimicrobial, serotonin agonists/antagonists and immunosuppressant drugs are associated with QT-prolongation. QT-interval prolongation and the consequent life-threatening Torsade de Pointes may develop in both outpatient and inpatient setting, however, the risk is thought to be higher among hospitalized patients. This is mainly because admitted patients usually receive multiple drugs and may have other risk factors, including electrolyte disturbances and hepatic or renal impairment.

Aim of the study:

This study is an attempt to address the issue of QT-prolongation and its prevalence among hospitalized patients, and evaluate the safety of prescribing patterns of QT-prolonging drugs selected in the study. The aim is to determine which drugs physicians more commonly prescribe and whether or not they cause long QT-interval in patients. Our paper also aims to provide general recommendations for a safer practice. We aim to extend the current knowledge and highlight this overlooked adverse effect in the clinical practice.

Methods:

This retrospective study was conducted based on electronic health records (EHRs). The Institutional Review Board (IRB) of Johns Hopkins Aramco Hospital approved the study. The data were extracted from EPIC healthcare system at Johns Hopkins Aramco Healthcare (JHAH) in Dhahran, Saudi Arabia over three-month period (December 1, 2019 to February 30, 2020). QTc values were calculated using Bazett equation. The study involved 122 hospitalized patients. We excluded pediatric

patients (≤18 years old) and pregnant women from our study. Six drug classes were chosen to be investigated: antiemetic serotonin antagonist (ondansetron), antiarrhythmic (amiodarone), fluoroquinolone antibiotics (ciprofloxacin, levofloxacin), macrolide antibiotics (erythromycin, azithromycin, clarithromycin), antihistamine (loratadine, cetirizine), antipsychotic drugs (haloperidol, quetiapine). The statistical software program GraphPad Prism 9.0.0 version was used to analyze and generate the figures.

Results:

Nearly half of them (51.6%) were arrhythmic patients. The duration of therapy was also considered, and we found that the majority of patients were on a short-term therapy (76.2%). Two-drug regimen was the most commonly observed (46.6% of patients), whereas nearly 30% were prescribed three or more QT-prolonging drugs. In respect to drug classes, the serotonin antagonist drug (ondansetron) was the most commonly prescribed agent among our patient population (69.6%). The corrected QT-interval (ECG reading) varied among patients; however, all subjects experienced QT-prolongation with varying degrees. Fifty-five per cent of patients fell into the 440-469 ms category, 22.9% were borderline (470-499 millisecond) and 12.3% had a clinically significant long QT syndrome (≥500 millisecond).

CONCLUSION:

A substantial number of patients presented with drug-induced QT prolongation with varying degrees. Scores of ≤500 ms does not mean nor eliminate the risk of developing fatal arrhythmias. Proper considerations are needed in order to optimize and minimize the use of drugs that are associated with long QT syndrome. This adverse effect usually goes undetected in real-world practice. ECG monitoring should be recommended in patients who are receiving two or more QT-prolonging drugs, elderly, and/or have other risk factors.

INTRODUCTION

Long QT syndrome is a disorder of the electrical impulses of the myocardium (myocardial repolarization). It is characterized by a prolonged QT-interval detected on ECG (electrocardiogram).[1] Many cut-offs have been suggested for long QT syndrome, but it is broadly defined as a QTc greater than 440 milliseconds.[11] Corrected QT-interval (QTc) value is calculated using the Bazett's formula:[13]

$$QTc = QT \div \sqrt{RR}$$

Long QT syndrome, or simply LQTS, is classified into two main types: congenital (primary) and acquired (secondary). Medications such as antibiotics, antiarrhythmic, antidepressants/antipsychotics, antiemetics, and anesthetic drugs may cause acquired LQTS. QT-prolongation can also be associated with electrolyte abnormalities

(hypokalemia and hypomagnesaemia), hypertrophic cardiomyopathy, severe malnutrition, and subarachnoid hemorrhage and other intracranial catastrophes.[1] Genetic polymorphisms (or mutations) also play an important role in the increased risk of QT-prolongation. Several types of congenital long QT syndrome and polymorphisms have been identified. The most common types are LQTS 1 and 2 (comprise >60% of LQTS cases). These patients have polymorphism in genes that encode for KCNQ1 and KCNH2, decreased Ikr (rectifier potassium channel) function and thus, predisposing them to LQTS and sudden death.[11]

This syndrome (LQTS) is associated with a significant increase in risk of a fatal arrhythmia called 'Torsade de Pointes (TdP)', a polymorphic ventricular tachycardia. A unique characteristic of TdP is the 'twisting of the peaks' pattern of the QRS complex. Patients who develop long QT syndrome will experience symptoms including tachycardia, seizures, syncope, and sudden death. LQTS-associated syncope typically occurs abruptly and without warning signs.[14]

Within the past two decades, several drugs have been withdrawn from the market in numerous countries as a result of sudden deaths from TdP, including astemizole, cisapride and terfenadine. These unfortunate incidences have led the pharmaceutical industry to intensify research and develop guidelines for drug assessments and their effect on the QT-interval.[12] Nevertheless, many medications remain available in the market and have the potential to cause long QT syndrome.[11]

Causes of acquired QT prolongation:
Medications: Anti-arrhythmic drugs (TdP reported in all), Calcium channel blockers, Psychiatric drugs, Antihistamine, Antimicrobial and antimalarial drugs, Immunosuppressant:

Risk factor:
The long QT syndrome can be considered an idiosyncratic event, however, a number of risk factors have been identified. These include:[5]
Large doses of QT-prolonging drugs
Rapid administration of QT-prolonging drugs via intravenous route.
Concomitant use of two or more QT-prolonging drugs
Presence of QT prolongation at baseline, ECG abnormalities or T wave lability
Hypokalemia, hypomagnesaemia, and other electrolyte disturbances
Renal or hepatic dysfunction
Polymorphism
Structural heart disease
Bradyarrhythmias
Gender (female sex) is a powerful predictor
Advanced age

QT-prolongation could be prevented by:
Avoiding the use of large doses (or overdose) of QT-prolonging drugs

Drugs known to cause LQTS should be avoided in patients with underlying cardiovascular disease, history of cardiac (ventricular) arrhythmia, electrolyte disturbance and other associated risk factors

Concurrent use of cytochrome P450 inhibitor drugs should be avoided (i.e. macrolide antibiotics, imidazole antifungals)

Avoiding the use of drugs that cause electrolyte disturbance

Serum potassium level monitoring should be recommended as routine care for patients on any potassium-depleting drugs.

ECG monitoring at baseline and after initiation or increment in dosage of a drug that is known to cause LQTS.

All drugs available have the potential to cause adverse effects to patients. Some serious adverse effects occasionally go undetected in the pre-clinical studies phase, and only become apparent when the drug reaches the market and is being used in clinical practice, which could result in different types of loss. This had led regulatory authorities to intensify their efforts on detecting drug-induced QT-prolongation in drug development phase.[4] Some non-cardiovascular medications have been removed from the market because they caused an increase in the QT-interval (as small as 5-10 milliseconds) and a resultant Torsade de Pointes.[6]

The proposed underlying mechanism of drug-induced long QT syndrome is the blockade of outward potassium movement, leading to a delay in repolarization and thus, prolonged action potential.[15] Torsade de Pointes (TdP) can occur in the setting of heart block and other cardiac diseases, however, it is more commonly seen in patients with either congenital LQTS or due to drug therapy.

Although some patients are healthy and do not possess any risk factors related to QT prolongation, the risk of developing fatal arrhythmia (TdP) remains high in the presence of drug interactions. These drug interactions can be either a pharmacodynamics or pharmacokinetic interaction. A combination of two or more QT-prolonging drugs (pharmacodynamics interaction) is the straightforward type. Prolongation in the QT-interval is due to the additive or synergistic effect on repolarization. The concomitant use of amitriptyline and haloperidol in psychiatric patients is one example. The likelihood life-threatening arrhythmias increase with higher doses. The second type (pharmacokinetic interaction) involves the use of a drug (or drugs) that increase the blood concentration of a QT-prolonging drug by interfering with hepatic metabolism (i.e. cytochrome P450 inhibition/induction).[7]

Aim of the study:
This study is an attempt to address the issue of QT-prolongation and its prevalence among hospitalized patients, and evaluate the safety of prescribing patterns of QT-prolonging drugs selected in the study. The aim is to determine which drugs physicians more commonly prescribe and whether or not they cause long QT-interval in patients. Our paper also aims to provide general recommendations for a safer

practice. We aim to extend the current knowledge and highlight this overlooked adverse effect in the clinical practice.

Methods:

This retrospective study was conducted based on electronic health records (EHRs). The Institutional Review Board (IRB) of Johns Hopkins Aramco Hospital approved the study. The data were extracted from EPIC healthcare system at Johns Hopkins Aramco Healthcare (JHAH) in Dhahran, Saudi Arabia over three-month period (December 1, 2019 to February 30, 2020). QTc values were calculated using Bazett equation. The study involved 122 hospitalized patients. We excluded pediatric patients (≤18 years old) and pregnant women from our study. Six drug classes were chosen to be investigated: antiemetic serotonin antagonist (ondansetron), antiarrhythmic (amiodarone), fluoroquinolone antibiotics (ciprofloxacin, levofloxacin), macrolide antibiotics (erythromycin, azithromycin, clarithromycin), antihistamine (loratadine, cetirizine), antipsychotic drugs (haloperidol, quetiapine). The statistical software program GraphPad Prism 9.0.0 version was used to analyze and generate the figures.

RESULTS:

Among the 122 patients included in the study, 58.6% were male, and 42.5% were female patients. Most of the subjects enrolled were elderly patients, with an average age of 69 years. In terms of weight, 42.7% of patients weighed <60 kg, while only 14.6% were over 100 kg. Patients were further classified into two groups, whether or not they had a history of cardiac arrhythmia. Nearly half of them (51.6%) were arrhythmic patients. The duration of therapy was also considered, and we found that the majority of patients were on a short-term therapy (76.2%). Two-drug regimen was the most commonly observed (46.6% of patients), whereas nearly 30% were prescribed three or more QT-prolonging drugs. In respect to drug classes, the serotonin antagonist drug (ondansetron) was the most commonly prescribed agent among our patient population (69.6%). The corrected QT-interval (ECG reading) varied among patients; however, all subjects experienced QT-prolongation with varying degrees. Fifty-five per cent of patients fell into the 440-469 ms category, 22.9% were borderline (470-499 millisecond) and 12.3% had a clinically significant long QT syndrome (≥500 millisecond).

Table (1): gender, age, weight, height, Height, Nationality and No. of prescribed QT-prolonging drugs among the studied cases

Variables	Patients n (%)	Mean ± SD
Gender		
Male	70 (58.6)	
Female	52 (42.5)	
Age		69.16 ± 13.62
<40	4 (3.27)	

40-49	4 (3.27)	
50-59	19 (15.57)	
60-69	29 (23.77)	
70-79	42 (34.42)	
80-89	19 (15.57)	
≥90	5 (4.09)	
Weight (kg)		72.42 ± 19.91
<60	34 (27.86)	
60-69	27 (22.13)	
70-79	13 (10.65)	
80-89	23 (18.85)	
90-99	12 (9.83)	
≥100	13 (10.65)	
BMI (metric)		28.09 ± 6.85
<18.5	11 (9.01)	
18.5-24.9	36 (29.50)	
25.0-29.9	25 (20.49)	
≥30	50 (40.98)	
Height (cm)		159.35 ± 13.93
Nationality		
Saudi	119 (97.5)	
Other	3 (2.5)	
No. of prescribed QT-prolonging drugs		
1	28 (22.9)	
2	56 (45.9)	
≥3	35 (28.6)	
CrCl (mL/min)		49.03 ± 27.81

Patients with History of Cardiac arrhythmia (%):

48.36% 51.63%

Yes (n=63)
No (n=59)
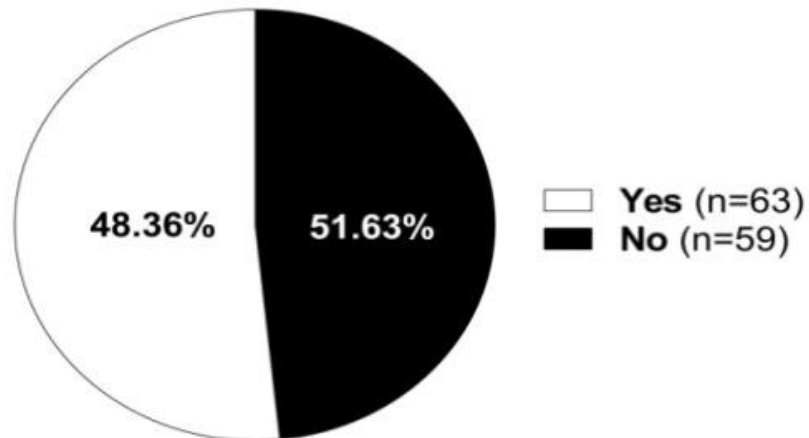
Fig. (1) shows the presence of underlying cardiac disease (arrhythmia)

Nearly half of our patients (51.63%) were healthy and free from cardiac diseases, whereas 48.36% of them were arrhythmic patients on antiarrhythmic drugs.
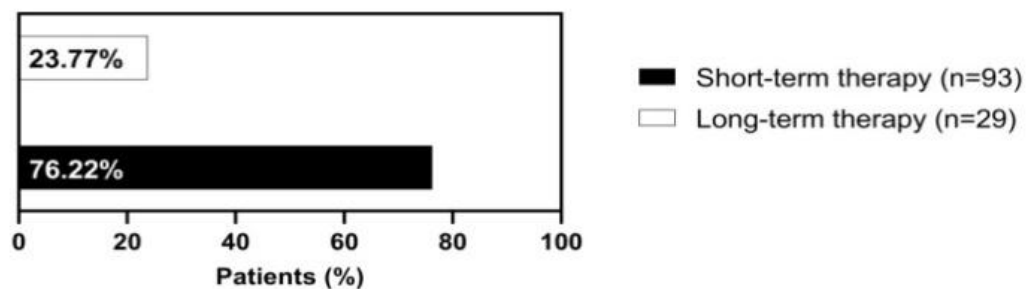
Duration of therapy:

23.77%

76.22%

Patients (%)

Short-term therapy (n=93)
Long-term therapy (n=29)

Fig. (2) Shows the duration of therapy: Out of 122 patients, 93 patients (76.22%) used QT-prolonging drugs for a short period only, and 29 patients (23.77%) were put on a long-term regimen.
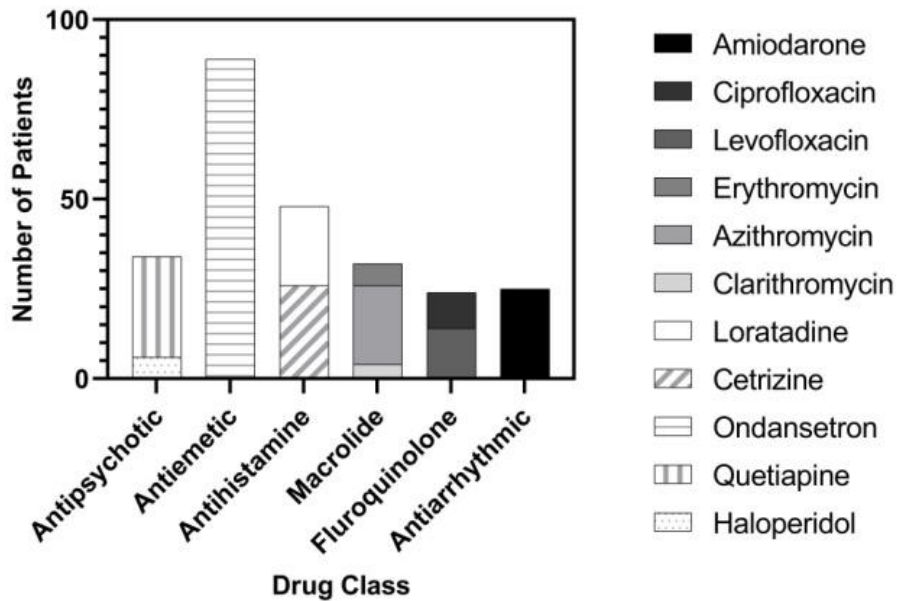
Fig. (3): shows the most common individual drugs in each class of patients. The antiemetic serotonin antagonist (ondansetron) was the most commonly prescribed medication among hospitalized patients. Around seventy per cent of them were given ondansetron either as combination with other agents or as monotherapy.
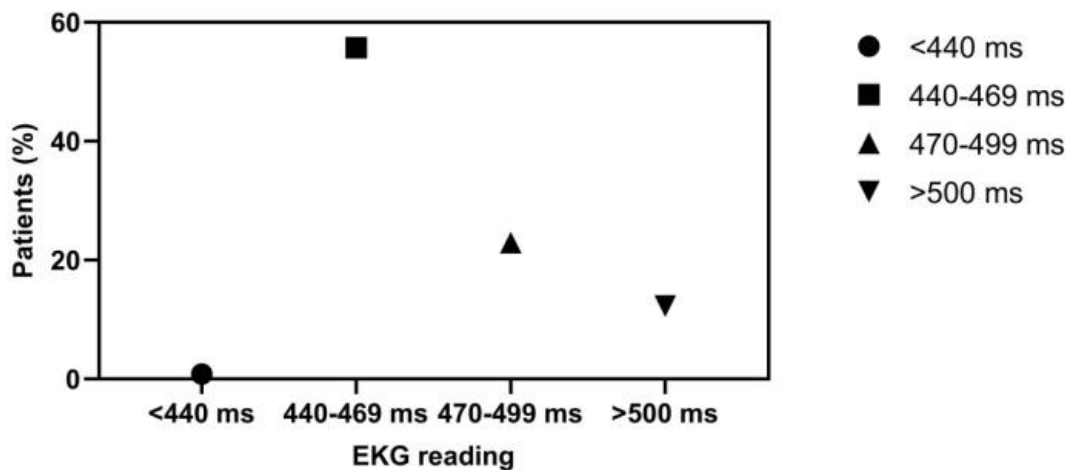

Fig. (4) Shows the ECG (QTc) reading of the patients. The corrected QT-interval (ECG reading) varied among patients; however, all subjects experienced QT-prolongation with varying degrees. Fifty-five per cent of patients fell into the 440-469 ms category, 22.9% were borderline (470-499 millisecond) and 12.3% had a clinically significant long QT syndrome (≥500 millisecond).
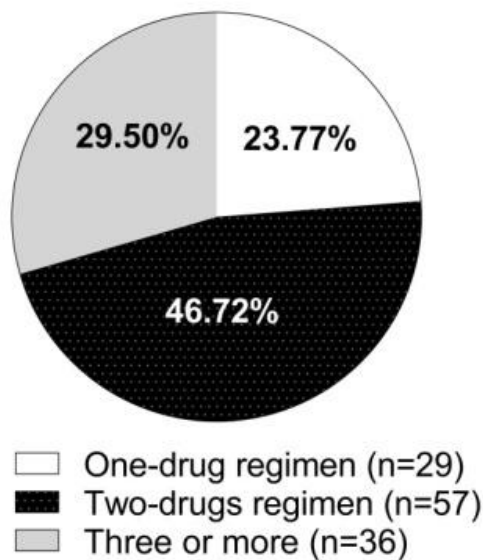
Types of Drug Regimens:

One-drug regimen (n=29) — 23.77%
Two-drugs regimen (n=57) — 46.72%
Three or more (n=36) — 29.50%

Fig. (5) shows the number of QT prolonging drugs prescribed for individual patients.

DISCUSSION:

A regimen containing two QT prolonging drugs was the most commonly seen (in 46.6% of patients), whereas nearly 30% were prescribed three or more QT-prolonging drugs. Only 24.7% patients were taking a single drug associated with LQTS.

In this study we found that the majority of patients were on a short-term therapy (76.2%). Two-drug regimen was the most commonly observed (46.6% of patients), whereas nearly 30% were prescribed three or more QT-prolonging drugs. In respect to drug classes, the serotonin antagonist drug (ondansetron) was the most commonly prescribed agent among our patient population (69.6%). In another study where Ninety (73.8%) patients were treated with azithromycin (usually in combination with ceftriaxone), and 32 (26.2%) patients with other antibiotics (ampicillin–clavulanate, chloramphenicol, doxcycline, or ceftriaxone); 72.1% (88) of the cohort experienced QT lengthening; 72.7% with QT lengthening had a normal baseline QTc. Azithromycin was not associated with the post-antibiotic QTc. Wide (pathological) post-antibiotic QTc was associated with the pneumonia score (17). While Saleh .M. etal reported that two hundred one patients were treated for coronavirus disease 2019 with chloroquine/hydroxychloroquine. Ten patients (5.0%) received chloroquine, 191 (95.0%) received hydroxychloroquine, and 119 (59.2%) also received azithromycin. The primary outcome of torsade de pointes was not observed in the entire population. Baseline corrected QT interval intervals did not differ between patients treated with

chloroquine/hydroxychloroquine (monotherapy group) versus those treated with combination group (chloroquine/hydroxychloroquine and azithromycin; 440.6±24.9 versus 439.9±24.7 ms, *P*=0.834)(18). Khan, Q. etal mentioned that in his study the most frequent QT prolonging risk factors included use of ≥1 QT prolonging drugs (74.5%), female gender (55%) and diabetes mellitus (36.3%). Total 487 QT prolonging drugs were identified. According to AZCERT classification, 33.8% of the interacting drugs were included in list-1 (known risk of TdP), 0.9% in list-2 (possible risk of TdP) and 58.8% in list-3 (conditional risk of TdP). (19). In another study 83% of the cases received at least one and up to eight QT-prolonging drugs at the same time. Combination of drugs with a known or possible risk for TdP (according to the AZCERT) was detected in 13,670 cases (50%). Most frequently prescribed psychotropic high-risk drugs ($n=48,995$) were the antipsychotics pipamperone ($n=6202$), quetiapine ($n=5718$), prothipendyl ($n=4298$), and risperidone ($n=4265$)(20).

In this study the corrected QT-interval (ECG reading) varied among patients, however, all subjects experienced QT-prolongation with varying degrees. Fifty-five per cent of patients fell into the 440-469 ms category, 22.9% were borderline (470-499 millisecond) and 12.3% had a clinically significant long QT syndrome (≥500 millisecond).
Every 10-point increase in the pneumonia score raised the risk for a pathological post antibiotic QTc by 1.249 (95%CI: 1.050–1.486). Analysis of patients with non-pathological baseline QTc revealed that pathological post-antibiotic QTc was only associated with previous stroke and not with the type of antibiotic.(17)

In another study the maximum corrected QT interval during treatment was significantly longer in the combination group versus the monotherapy group (470.4±45.0 ms versus 453.3±37.0 ms, *P*=0.004). Seven patients (3.5%) required discontinuation of these medications due to corrected QT interval prolongation. No arrhythmogenic deaths were reported.(18)

Khan Q. etal reported that the occurrence of QT-DDIs was significantly associated with ≥10 prescribed medications (p = 0.01), chronic liver disease (p = 0.05), chronic obstructive pulmonary disease (p = 0.03), gastroenteritis (p = 0.02), antimicrobials (p < 0.001), antiemetics (p < 0.001) and antinausea (p < 0.001)(19).

The replacement of high-risk drugs such as tricyclic antidepressants, levomepromazine, melperone, and promethazine with more tolerable drugs could avoid 11% of QT-prolonging drugs and increase the tolerability of psychopharmacological treatment. More than 80% of psychiatric patients receive at least one QT-prolonging drug during their hospital stay, and almost 50% of these drugs are combined in clinical practice. For the prevention of cardiac ADRs, the physician should evaluate the risk for QT prolongation for each drug and patient-specific risk factors before prescribing these drugs or drug combinations(20).

CONCLUSION:

A substantial number of patients presented with drug-induced QT prolongation with varying degrees. Scores of ≤500 ms does not mean nor eliminate the risk of developing fatal arrhythmias. Proper considerations are needed in order to optimize and minimize the use of drugs that are associated with long QT syndrome. This adverse effect usually goes undetected in real-world practice. ECG monitoring should be recommended in patients who are receiving two or more QT-prolonging drugs, elderly, and/or have other risk factors.

REFERENCES

1. Yee Guan Yap, A John Camm. Drug induced QT prolongation and torsades de pointes. Heart J. 2003; 89(11):1363–1372.
2. Acquired long QT syndrome: Definitions, causes, and pathophysiology. UpToDate; 2019 (https://www.uptodate.com/contents/acquired-long-qt-syndrome-definitions-causes-and-pathophysiology, accessed October 2019)
3. Dan M. Roden. Drug-Induced Prolongation of the QT Interval. N Engl J Med. 2004; 350:1013–22.
4. Barbara A. Liu, David N. Juurlink. Drugs and the QT Interval. N Engl J Med. 351;11.
5. Drug induced QT prolongation. NHS Greater Glasgow and Clyde Medicines Information Service; 2012 (https://ggcmedicines.org.uk/media/uploads/ps_extra/pse_21.pdf, accessed October 2019)
6. Jamie L. Thompson. Drug-Induced QT Prolongation. US Pharmacist J. 2007.
7. Yap YG, Camm AJ. Drug induced QT prolongation and torsades de pointes. Heart J. 2003; 89:1363-1372.
8. Farzam K, Tivakaran VS. QT Prolonging Drugs. Statpearls J. 2020.
9. Nachimuthu S, Assar, Schussler JM. Drug-induced QT interval prolongation: mechanisms and clinical management. Ther Adv Drug Saf. 2012; 3(5):241–253.
10. Clinical relevance and management of drug-related QT interval prolongation. Pharmacotherapy. 2003; 23(7):881–908.

11. Katy E. Trinkley, Robert Lee Page II, Hoang Lien, Kevin Yamanouye & James E. Tisdale. QT interval prolongation and the risk of torsades de pointes: essentials for clinicians. Current Medical Research and Opinion. 2013; 29:12, 1719-1726.

12. Isbister GK, Page CB. Drug induced QT prolongation: the measurement and assessment of the QT interval in clinical practice. Br J Clin Pharmacol. 2013 Jul;76(1):48-57.

13. Khan Q, Ismail M, Haider I, Haq IU, Noor S. QT interval prolongation in hospitalized patients on cardiology wards: a prospective observational study. Eur J Clin Pharmacol. 2017 Nov;73(11):1511-1518.

14. Shah SR, Park K, Alweis R. Long QT Syndrome: A Comprehensive Review of the Literature and Current Evidence. Current Problems in Cardiology. 2019 Mar;44(3):92-106.

15. Cahoon WD Jr. Acquired QT prolongation. Progress in Cardiovascular Nursing. 2009 Mar;24(1):30-33.

16. Ojero-Senard A, Benevent J, Bondon-Guitton E, Durrieu G, Chebane L, Araujo M, Montastruc F, Montastruc JL. A comparative study of QT prolongation with serotonin reuptake inhibitors. Psychopharmacology (Berl). 2017 Oct;234(20):3075-3081.