QT Interval Prolongation and the Risk of Torsades de Pointes: Essentials for Clinicians.

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Review

QT interval prolongation and the risk of torsades de pointes: essentials for clinicians

Katy E. Trinkley
Robert Lee Page II
Hoang Lien
Kevin Yamanouye
University of Colorado, Skaggs School of Pharmacy and Pharmaceutical Sciences, Aurora, CO, USA

James E. Tisdale
College of Pharmacy, Purdue University, West Lafayette, IN, USA

Address for correspondence:
Katy E. Trinkley PharmD, Assistant Professor, Department of Clinical Pharmacy, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of Colorado, Anschutz Medical Campus, 12850 E Montview Blvd., Mail Stop C238, Aurora, CO 80045, USA.
Tel.: +1 303 724 6563; Fax: +1 303 724 0979;
Katy.Trinkley@ucdenver.edu

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Abstract

Objective:
QT interval prolongation signifies an increased risk of the life-threatening arrhythmia torsades de pointes (TdP). The purpose of this paper is to review the diverse methods for assessing and monitoring the risk of TdP, discuss risk factors for TdP, and recommend interventions that may mitigate the risk of TdP.

Methods:
A non-systematic search of PubMed (through March 2013) was conducted to determine the optimal approach to assessing and monitoring QT interval, prevention of TdP, and to identify risks factors for TdP. Papers known to the authors were included, as were scientific statements. Articles were chosen based on the judgment of the authors.

Results:
Risk factors for drug-induced TdP include hypokalemia, female sex, drug–drug interactions, advancing age, genetic predisposition, hypomagnesemia, heart failure, bradycardia, and corrected QT (QTc) interval prolongation. Many risk factors, including hypokalemia, use of QT-interval-prolonging drugs, and drug interactions are potentially modifiable and should be corrected in persons at risk for QT interval prolongation. Given the variable onset of TdP following initiation of QT-interval-prolonging drugs, careful and regular monitoring of electrocardiography (EKG) and electrolytes are necessary. Patients at risk for QT interval prolongation should be educated to go directly to the emergency room if they experience palpitations, lightheadedness, dizziness or syncope. When the QTc interval is 470–500 ms for males, or 480–500 ms for females, or the QTc interval increases 60 ms or more from pretreatment values, dose reduction or discontinuation of the offending drug should be considered where possible, and electrolytes corrected as needed. Furthermore, if the QTc interval is $\geq$500 ms, the offending drug should be discontinued, and continuous EKG telemetry monitoring should be performed, or the 12-lead EKG should be repeated every 2–4 hours, until the QT interval has normalized.

Conclusions:
Close monitoring for QTc prolongation is necessary to prevent TdP. The recommendations in this paper are limited by the available evidence and additional studies are needed to better define the approach to monitoring.

Introduction

QT interval prolongation can lead to the ventricular arrhythmia known as torsades de pointes (TdP), which can result in sudden cardiac death. In recent years, the potential for QT interval prolongation and TdP has received increased attention, partly owing to increased recognition of the risks and catastrophic nature of this disease[1–3]. Although the risk of QT interval prolongation and resultant life threatening TdP may be present in both outpatients and inpatients, hospitalized patients are thought to be at a greater risk, given they are more likely to have a larger number of risk factors, such as electrolyte abnormalities, kidney

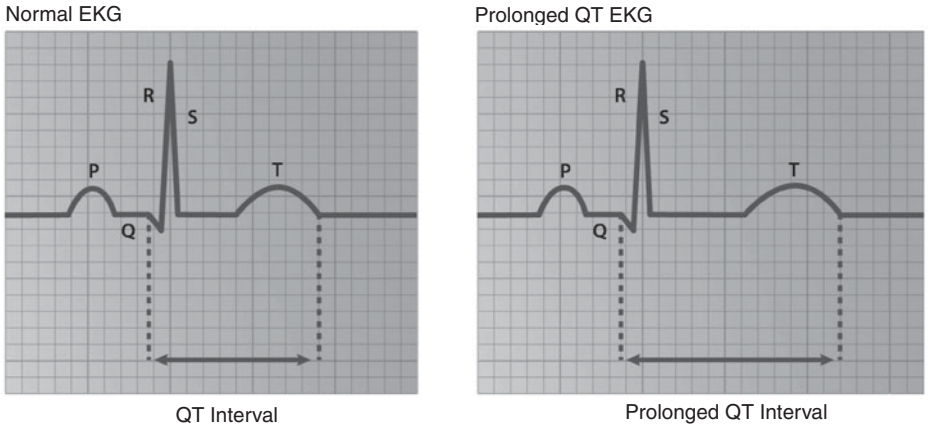

Figure 1. EKG of a normal QT interval and a prolonged QT interval.

disease, and cardiovascular disease[1]. A prospective, observational study of patients admitted to cardiac critical care units found nearly 30% of patients had QT interval prolongation upon admission, and of those, 35% were subsequently administered a QT-interval-prolonging drug[4]. Administering a QT-interval-prolonging drug to a person with known QT prolongation greatly increases the risk of TdP, especially in the presence of other risk factors[1].

Within the past 15–20 years, numerous medications, including terfenadine, astemizole and cisapride have been removed from the United States (US) market as a result of inducing deaths from TdP. However, many drugs with the potential to cause QT interval prolongation remain available[5]. In view of the large number of medications available that may prolong the QT interval, and the frequency of QT interval prolongation, clinicians should be aware of the risks associated with QT interval prolongation and TdP. The purpose of this paper is to review the diverse methods for assessing and monitoring the risk of TdP, discuss risk factors for TdP, and recommend interventions that may mitigate the risk of TdP.

Methods

A non-systematic search of PubMed (up to March 2013) was conducted to determine the optimal approach to assessing and monitoring QT interval, prevention of TdP, and to identify risks factors for TdP. Papers known to the authors were included, as were international recommendation statements. Articles were chosen based on the judgment of the authors.

QT interval prolongation and TdP

A prolonged QT interval is defined by AHA/ACCF as a rate-corrected QT (QTc) interval greater than the 99th percentile for females and males, which is >480 ms and >470 ms, respectively[1]. However, many standard EKGs continue to label a QTc interval of >440 ms as borderline QTc interval prolongation[1]. A prolonged QTc interval represents the prolongation of the repolarization phase of the ventricular action potential[6]. TdP is a polymorphic ventricular tachycardia characterized by a pattern of twisting of the peaks (or 'points') of the QRS complexes[1]. Figure 1 is an example of EKGs indicating a normal and prolonged QT interval. A prolonged QTc on an EKG is an indicator of prolonged ventricular repolarization[1], which increases the risk of TdP and resultant sudden cardiac death. Prolonged repolarization can be mediated via several subtypes of sodium and potassium channels in cardiac myocytes. Most commonly, acquired prolongation of repolarization is caused by inhibition of the rapid component of the delayed rectifier potassium current (I_{Kr})[6].

Measuring QT interval prolongation as a predictor of TdP

Progressive prolongation of the QTc interval increases the risk for TdP, and the risk increases markedly when the QTc interval exceeds 500 ms[7]. Despite this, limitations exist when using QTc interval prolongation as a surrogate marker for TdP, complicating monitoring and risk stratification. Not every patient that develops QTc interval prolongation, even beyond 500 ms, experiences TdP. Therefore, while progressive increases in QTc interval increase the risk, QTc interval prolongation is an imperfect predictor of TdP. In addition, obtaining an accurate QTc measurement is difficult, and measurement and rate correction of QTc intervals is often performed incorrectly[8]. Many factors influence QTc interval measurements, including interindividual variability in performing measurements, diurnal variability and heart rate. Diurnal variability in QT intervals can be as much as 100 ms[3]. Although the influence of heart rate on the QT interval can be minimized by calculations that correct for

RR interval, there are many different calculations for correcting the QT interval that each result in different values. The most commonly used equation for calculating the corrected QT interval is Bazett's formula (QTc = QT interval/√[RR interval]), which was developed in 1920[9]. Although most EKG machines automatically correct the QT interval using Bazett's equation, it is prudent for clinicians to manually measure and calculate the QTc, as technologies are not fail-proof[10]. Bazett's formula is accepted as the correction factor for use in clinical practice; however, this method is known to overcorrect the QT interval at fast heart rates and undercorrect at slow heart rates, leading to falsely prolonged or shortened QTc intervals, respectively. Other QT interval corrections exist (e.g., Fridericia, Van de Water), and, while used for research purposes, are not commonly used in clinical practice[11]. Despite the limitations of Bazett's formula, it continues to be that which is most commonly used for QT interval correction in clinical practice[12].

QTc interval prolongation as a predictor of TdP

Despite inconsistency in the predictive ability of the QTc interval, the lack of a better predictive method of detecting TdP warrants its continued use. To increase reliability of the QTc interval measurement, only highly trained individuals should perform the measurement, or the measurement should be automatically generated by the EKG machine using a universally accepted definition for QTc interval prolongation. When using the QTc interval as a predictor of TdP, the magnitude of the QTc interval and the magnitude of the QTc interval increase can be useful in understanding the risk of TdP. For each 10 ms increase in the QTc interval, there is roughly a 5–7% increase in the risk of developing TdP[7,13], and every 20 ms increase in QTc substantially increases the risk of TdP[14]. QTc interval prolongation is generally defined as greater than 480 ms in women and greater than 470 ms in men, and a QTc interval ≥500 ms is widely considered the point at which the risk of TdP is very high and intervention is needed[1].

Risk factors for TdP

Prolonged QTc interval can be the result of extrinsic causes (e.g., drugs, hypokalemia, bradycardia) or a genetic predisposition (the congenital long QT syndrome, or LQTS). Table 1 lists common risk factors for TdP. There is a risk of sudden cardiovascular death regardless of whether QTc interval prolongation resulted from an extrinsic cause or LQTS, warranting caution in both scenarios. Further, all potential causes for QTc interval prolongation are considered to be risk factors for TdP. Risk factors for acquired QTc interval prolongation include electrolyte disturbances, structural heart disease, bradycardia, female sex, advanced age, history of QTc prolongation, genetic polymorphisms, and drugs[6]. Hypokalemia inhibits I_{Kr}, leading to prolongation of repolarization. Hypomagnesemia impairs the function of the sodium–potassium ATPase pump, leading to reduced intramyocyte potassium concentrations[15]. Females are more susceptible to drug-induced inhibition of I_{Kr} and have inherently longer QTc intervals than adult males, which predisposes females to QTc interval prolongation and TdP. Structural heart disease, including myocardial infarction and heart failure, is a risk factor for TdP[16].

Table 1. Non-drug risk factors for QT interval prolongation.

Hypokalemia	Structural heart disease	History of QTc prolongation
Bradycardia	Bradycardia	Genetic polymorphisms
Congenital long QT syndrome	Female sex	Hypomagnesemia
Long QT syndrome	Advanced age	Hypocalcemia

QTc = corrected QT.

Genetic risk factors for TdP

Genetic mutations and polymorphisms also increase the risk of QTc interval prolongation. Numerous such polymorphisms have been identified, and multiple types of congenital LQTS have been identified, with LQTS 1 and 2 the most common. LQTS 1 and 2 comprise more than 60% of congenital LQTS cases and are the result of polymorphisms in genes that encode for I_{Kr}, KCNQ1 and KCNH2[1,17]. Patients with these polymorphisms have decreased I_{Kr} function, which may lead to LQTS, increasing the risk of TdP and possible sudden death. There is some evidence that 10–15% of patients who experience drug-induced TdP may have a genetic predisposition in the form of mutations or polymorphisms of genes that are associated with the congenital LQTS[18]. Although QT-interval-prolonging drugs can increase the risk of QTc interval prolongation and TdP, QT-interval-prolonging drugs rarely cause TdP in the absence of other TdP risk factors. Nearly all cases of drug induced QTc interval prolongation occur in the presence of at least one known risk factor and over 70% occur in the presence of ≥2 risk factors[16].

Drug-induced TdP

The risk of drug-induced QTc interval prolongation varies by drug and presence of risk factors. The drugs of greatest concern are those that not only increase the QTc interval, but that have also been associated with TdP, compared to drugs that have only demonstrated an increase in the QTc interval. Although most drugs that prolong the QTc interval have documented reports of TdP, not all drugs that

prolong the QTc interval have yet been associated with TdP in published reports. The risk of QTc interval prolongation is often greater in association with intravenous administration, presumably as a result of higher plasma drug concentrations and greater cardiovascular exposure[1]. Similarly, the dose of a QTc prolonging drug also influences the risk of QTc prolongation. Although not always the case, higher doses are often associated with increased risk of QTc prolongation. Drugs for which doses are not appropriately adjusted for kidney or liver disease can increase the risk of QTc interval prolongation if plasma concentrations become supratherapeutic. In addition, drug–drug interactions leading to supratherapeutic plasma concentrations of a QTc-interval-prolonging drug can be an important risk factor for QTc interval prolongation. In particular, cytochrome P450 (CYP450) mediated drug interactions can lead to clinically significant plasma drug concentration changes. Strong CYP450 inhibitors may increase the area under the curve (AUC) of the substrate by five-fold or greater or decrease clearance by 80%, whereas moderate inhibitors may increase the AUC of the substrate by two- to five-fold or decrease clearance by 50–80%[19]. These effects can lead to elevations in plasma concentrations of drugs sufficient to result in QTc interval prolongation. Table 2 lists some common CYP450 inhibitors.

Drugs associated with QTc interval prolongation and TdP

Drugs known to cause TdP are listed in Table 3. Some drugs that have recently received increased attention as a result of prolonging the QTc interval and increasing the risk of TdP include citalopram, escitalopram, methadone, ondansetron and azithromycin.

Citalopram and escitalopram

In 2011, the FDA released an announcement stating that both citalopram and escitalopram cause QTc interval prolongation in a dose-dependent fashion, an effect which was determined to be clinically significant for citalopram at the 60 mg dose[20]. This announcement was based on postmarketing reports of prolonged QTc interval and cases of TdP that were further supported by a prospective, double blind, randomized crossover trial. Citalopram was found to increase the QTc interval by 8.5 ms and 18.5 ms, at 20 mg and 60 mg doses, respectively, whereas escitalopram increased the QTc interval by 4.5 ms and 6.5 ms, at 10 mg and 60 mg doses, respectively. Given these results and the lack of additional

Table 3. Drugs associated with torsades de pointes.

Amantadine	Diphenhydramine	Ibutilide	Quetiapine
Amiodarone	Dofetilide	Ketoconazole	Risperidone
Amitriptyline	Doxepin	Levofloxacin	Sotalol
Azithromycin	Erythromycin	Methadone	Tacrolimus
Chlorpromazine	Escitalopram	Moxifloxacin	Thioridazine
Ciprofloxacin	Fluconazole	Ondansetron	Trazodone
Citalopram	Fluoxetine	Pimozide	Trimethoprim-sulfamethoxazole
Clarithromycin	Granisetron	Procainamide	Voriconazole
Clozapine	Haloperidol	Quinidine	Ziprasidone

Table 2. Common cytochrome P450 inhibitors and QTc-interval-prolonging substrates[19].

	Strong inhibitors (≥5-fold increase in AUC)	Moderate inhibitors (>2 but <5-fold increase in AUC)	QTc-interval-prolonging drug substrates
CYP1A2	Ciprofloxacin, enoxacin, fluvoxamine	Mexiletine, oral contraceptives, phenylpropanolamine, thiabendazole, zileuton	Diphenhydramine, ondansetron, pimozide, ziprasidone
CYP2C8	Gemfibrozil		Amiodarone
CYP2C9		Amiodarone, fluconazole, miconazole, oxandrolone	Diphenhydramine, voriconazole
CYP2C19	Fluconazole, fluvoxamine, ticlopidine	Esomeprazole, fluoxetine, moclobemide, omeprazole, voriconazole	Citalopram, diphenhydramine, doxepine, escitalopram, methadone, fluoxetine, voriconazole
CYP3A4	Boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole	Amprenavir, aprepitant, atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, imatinib, verapamil	Amiodarone, citalopram, clarithromycin, dofetilide, erythromycin, escitalopram, ketoconazole, methadone, ondansetron, haloperidol, pimozide, quetiapine, tacrolimus, trazodone, voriconazole, ziprasidone
CYP2D6	Buproprion, fluoxetine, paroxetine, quinidine	Duloxetine, terbinafine	Citalopram, diphenhydramine, doxepine, escitalopram, ondansetron, fluoxetine, pimozide, risperidone

AUC = area under the curve; CYP = cytochrome.

benefit of citalopram at doses exceeding 40 mg daily, the FDA now recommends that citalopram daily doses be limited to 40 mg and lower doses are recommended for persons at high risk of QTc interval prolongation, including those older than 60 years of age. However, the FDA did not make any specific recommendations regarding escitalopram use and states that the QTc interval prolongation associated with escitalopram is not clinically significant. Since the release of the FDA's announcement, a retrospective, cross-sectional study of electronic health records confirmed the FDA's findings of dose-dependent QTc interval prolongation associated with both citalopram and escitalopram[21].

Methadone

In recent years, methadone has come under scrutiny due to its potential to cause QTc prolongation and increased risk for TdP. Several case reports have linked high-dose methadone with TdP. Of 43 cases of methadone-induced TdP reported to MedWatch, 8% were fatal and involved doses of methadone that exceeded 100 mg daily[22]. Given the risk of QTc prolongation and TdP with methadone, methadone's prescription label includes a black box warning regarding QTc interval prolongation and recommendations specific to monitoring methadone and its risk of QTc prolongation exist[23]. The recommendations for monitoring methadone are: 1) inform patients of the risks prior to initiation, 2) assess for history of structural heart disease, arrhythmia, and syncope, and 3) obtain an EKG at baseline, an EKG within 30 days of initiating methadone and annually[23].

Ondansetron

Multiple studies have considered the QTc-interval-prolonging potential of ondansetron. Of the six published studies, five found ondansetron to significantly increase the QTc interval up to 24.9 ms; however, there is only one published report of TdP, which occurred in a child with occult congenital LQTS[24]. Studies of oral ondansetron have not identified QT interval prolongation as an adverse effect.

In response to growing evidence that ondansetron increases the risk of QTc interval prolongation, the FDA required the manufacturer of ondansetron to conduct a study to assess the risk[25]. The preliminary results demonstrated that IV ondansetron increased the QTc interval by 6 to 8 ms with the 8 mg and 32 mg doses, respectively. These findings led to the 32 mg dose being removed from the package label and recommendations to not exceed 16 mg of intravenous ondansetron.

Azithromycin

Recently, azithromycin has been added to the growing list of drugs that can lead to QTc interval prolongation and TdP. Compared to other macrolides, azithromycin may pose a lower risk of TdP[26]. Of five case reports in the literature of azithromycin-induced QTc interval prolongation[27–31] three report TdP[27,28,31]. In these case reports, all patients had baseline risk factors for QTc interval prolongation (e.g., elderly, heart failure, bradycardia). Further, there is a report of polymorphic ventricular tachycardia in a person with a normal QT interval[32] and azithromycin was recently reported to increase the risk of sudden cardiac death, possibly as a result of TdP[33].

Preventing and mitigating the risk of QTc interval prolongation and TdP

The growing number of drugs associated with QTc interval prolongation as well as the sudden onset of TdP and its catastrophic nature warrant cautionary measures to prevent QTc interval prolongation and TdP. Recognizing risk factors for QTc interval prolongation and assessing a patient's risk for QTc interval prolongation are the first steps to decreasing the risk of TdP. Correcting any modifiable risk factors for QTc interval prolongation and avoiding additional risk factors are key to prevention.

Risk minimization of drug-induced QTc prolongation and TdP

Minimizing the risk of drug-induced QTc interval prolongation requires knowledge of the actual risk associated with specific drugs. There are many databases that provide information on QTc-interval-prolonging drugs, most notably the University of Arizona Center for Education and Research on Therapeutics' database (www.azcert.org). Table 4 summarizes an approach to preventing and mitigating the risk of drug-induced TdP. When initiating a QTc-interval-prolonging drug, patients must be screened for baseline risk factors. For patients at risk for QTc interval prolongation, drugs without potential to cause QTc interval prolongation should be used in place of QTc-interval-prolonging drugs whenever possible. The risk of QTc interval prolongation must be weighed against the benefits of using the QTc-interval-prolonging drug. When therapy with a QTc-interval-prolonging drug is necessary, the lowest effective dose should be used, ensuring appropriate adjustment for kidney or liver disease, as well as drug interactions.

For patients taking a QTc-interval-prolonging drug who have known risk factors, monitoring may be challenging, given the variable and unpredictable occurrence of

Table 4. Reducing the risks of drug-induced torsades de pointes.

Recommended for all high-risk patients	
Assess risk factors for QTc interval prolongation	Potentially modifiable risk factors: • Bradycardia • Hypomagnesemia • Hypokalemia • Hypocalcemia • Drugs that induce QTc interval prolongation (Table 2) Non-modifiable risk factors: • Myocardial infarction • Heart failure • Female sex • Age >65 years • Genetic polymorphism • History of QTc interval prolongation
Minimize risk factors	• Where possible, use alternative agents that do not prolong the QT interval • If QTc-interval-prolonging drugs are warranted, use lowest effective dose • Correct underlying causes of electrolyte abnormalities or drug-induced bradycardia
Educate patient	Instruct patient to contact their primary care provider, or go to the emergency room if they experience: • Palpitations • Lightheadedness • Dizziness • Syncope
Monitoring parameters	EKG • Baseline prior to initiation of QTc-interval-prolonging drug • Once QTc-interval-prolonging drug reaches steady state (5 half-lives) • Every month for 6 months, then every 6 to 12 months thereafter Electrolytes • Baseline prior to initiation of QTc-interval-prolonging drug • Once QT-interval-prolonging drug reaches steady state (5 half-lives) • Annually
When to modify therapy	**How to modify therapy**
• If baseline EKG shows QTc interval of 470–500 ms (males) or 480–500 ms (females)	• Consider discontinuing offending agent when an appropriate drug that does not cause QTc interval prolongation can be substituted
• If any follow-up EKG reveals an absolute increase in QTc ≥60 ms	• Correct electrolyte imbalances
• If follow up EKG reveals a QTc interval ≥500 ms	• Discontinue offending agent • Correct all electrolytes necessary. • *Additional follow-up EKG should be immediately repeated to ensure accuracy and then continuous EKG telemetry monitoring should be performed, or the 12-lead EKG should be repeated every 2–4 hours until normalized
• Torsades de pointes	• Discontinue offending drug(s) • Treat arrhythmia

*Most drugs should be monitored every 2–4 hours until the QTc is normalized; however, certain drugs with long half lives (e.g., amiodarone) may not require as frequent EKG monitoring.
EKG = electrocardiogram; QTc = corrected QT.

drug-induced TdP. The onset of TdP following administration of a QTc-interval-prolonging drug was within 72 hours in only 18% of persons, between days 3 and 30 in 42% and after 30 days in 40%[16]. Therefore, careful monitoring throughout the entire course of treatment is warranted. The authors' recommendations for monitoring should include baseline and periodic EKGs and electrolyte monitoring. Further, for high risk patients, monitoring of EKG and electrolytes ideally occurs when plasma concentrations of the QTc prolonging drug reach steady state, which is approximately five half-lives of the drug. This should be followed by repeat EKG measurements every month until month 6, and then every 6–12 months thereafter. If any follow-up EKG reveals a QTc interval between 470–500 ms in males or 480–500 ms in females, or an absolute increase in QTc interval of 60 ms, intervention may be needed, which may include discontinuation of the offending agent, where possible and appropriate, and/or correcting electrolyte imbalances. If any follow-up EKG reveals a QTc interval ≥500 ms, the offending agent

should be discontinued, electrolytes corrected as necessary and an additional follow up EKG ordered. All patients at risk of QTc interval prolongation should be educated to contact their provider if they experience palpitations, lightheadedness, dizziness, or syncope. Further, patients should be educated to inform their providers that they are taking a potentially QT prolonging drug and to not use any over-the-counter medications without consulting a pharmacist.

Risk minimization in hospitalized patients

As hospitalized patients may be at greater risk for drug-induced QTc interval prolongation and TdP[1] and often receive QTc-interval-prolonging drugs[4], risk assessment in that population is particularly important. There is a need for evidence-based QTc interval prolongation risk assessment tools for hospitalized patients. A risk score for QTc interval prolongation was developed and validated in patients admitted to coronary care units[34]. This risk score incorporates easily obtainable clinic risk factors including age, female sex, serum potassium, admitting QTc interval, comorbid conditions such as acute myocardial infarction and heart failure, and specific concomitant drug therapy to calculate a risk score and categorize patients' risk of QTc interval prolongation as low, moderate or high. Risk quantification methods such as this can be used to identify patients at highest risk for drug-induced QTc interval prolongation and target those patients for intense monitoring and/or substitution of non-QTc interval prolonging drugs in place of QTc interval prolonging drug therapy where possible and appropriate.

Conclusion

A prolonged QT interval can be a serious situation, due to its potential to lead to TdP and sudden cardiac death. Increased vigilance regarding QTc interval monitoring and risk mitigation strategies are needed in every patient care setting, including outpatient and inpatient services. However, hospitalized patients have the greatest risk of developing TdP due to the presence of other risk factors (e.g., electrolyte imbalance, structural heart disease, female sex). Meaningful vigilance of QTc interval prolongation and TdP requires appropriate assessment techniques, including the magnitude of QTc interval prolongation. The presence of multiple risk factors increases the risk of TdP; thus, identifying and minimizing risk factors is important to reduce the risk of TdP. Whenever possible, preventable risk factors should be ameliorated or their risk minimized. QTc-interval-prolonging drugs should be avoided in persons with risk factors, or used at the smallest effective dose with close EKG monitoring and patient vigilance for symptoms of TdP.

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