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УДЛИНЕНИЕ ИНТЕРВАЛА QTC: РОЛЬ ПОЛИПРАГМАЗИИ, ЛЕКАРСТВЕННОЕ ВЗАИМОДЕЙСТВИЕ И РЕКОМЕНДАЦИИ ДЛЯ КЛИНИЧЕСКОЙ ПРАКТИКИ

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Основные положения

• Приобретённый синдром удлинённого интервала QT – редкое заболевание, но частота встречаемости удлинения интервала QTc растёт при полипрагмазии.

Резюме

Приобретенный синдром удлиненного интервала QT является редким заболеванием. Однако частота встречаемости удлиненного интервала QTc увеличивается у пациентов с полипрагмазией. Риск как удлинения интервала QTc, так и тахикардии типа «пируэт» возрастает экспоненциально при одновременном применении нескольких препаратов, удлиняющих интервал QTc. В этой статье показаны механизмы, лежащие в основе заболевания и способы снижения риска потенциально фатальных аритмий.

Ключевые слова

Удлинение интервала QT • Лекарственно-индуцированное удлинение интервала QT • Побочные эффекты лекарственных средств • Тахикардия типа «пируэт» • Внезапная сердечная смерть

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АНАЛИТИЧЕСКИЙ ОБЗОР

QTC INTERVAL PROLONGATION: ROLE OF POLYPHARMACY, DRUG INTERACTION AND CONSIDERATIONS FOR CLINICAL PRACTICE

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Highlights

• Acquired long QT syndrome is a rare disease, but the frequency of QTc prolongation increases with polypragmasia.

Abstract

Acquired long QT syndrome is a rare condition. However, the prevalence of prolonged QTc interval increases among patients with polypharmacy. The risk of both QTc interval prolongation and torsades de pointes (TdP) tachycardia escalates exponentially with the concomitant use of multiple QTc-prolonging drugs. This article explores the underlying mechanisms of the condition and methods to mitigate the risk of potentially fatal arrhythmias.

Keywords

QT interval prolongation • Drug-induced QT prolongation • Drug side effects • Torsades de pointes • Sudden cardiac death

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Список сокращений

COPD	– chronic obstructive pulmonary disease	QTc F	– QTc time calculated using Fredericia's formula
ECG	– electrocardiogram	QTc Interval	– QT interval corrected for heart rate
mV	– millivolt	RR Distance	– distance between two QRS complexes
QTc B	– QTc time calculated using Bazett's formula	TdP	– torsades de Pointes

Introduction

In recent years the clinical cardiology community has paid increasing attention to QT interval prolongation as a risk factor for life-threatening polymorphic ventricular tachycardia [1, 2]. One of the causes of QT interval prolongation is the effect of medications. To avoid prescribing potentially dangerous drug combinations to patients with comorbid conditions, clinicians need to understand drug metabolism. Therefore, it is crucial to identify the most commonly used medications in outpatient clinical practice that affect the QT interval (not only with proven but also with probable and conditional risk of QT interval prolongation); drug combinations (with probable and conditional risk of QT interval prolongation among themselves), and combinations of medications with drugs that can influence the activity of the cytochrome P450 isoenzymes that metabolize them [3].

The aim of the review is to estimate potential risk-factors that are associated with QT interval prolongation.

QT interval prolongation can have dramatic consequences. The prognosis for such patients, particularly those taking several medications, is serious. Adverse clinical outcomes are linked to the risk of developing ventricular fibrillation or asystole [4, 5].

Pathophysiology

It is known that when describing an ECG, in some cases an unusual arrhythmia occurs, which is characterized by spontaneous bursts that cause dizziness or fainting, and sometimes convulsions. In certain cases, this arrhythmia can develop into ventricular fibrillation, leading to sudden cardiac death. The development of such significant changes is based on a slowdown in the repolarization process, which occurs due to the blockade of potassium channels, which is reflected on the ECG film in the form of an elongation of the QT interval [6, 7]. It is important to note that these processes can be triggered by taking medications (drugs), which should be taken into account in real clinical practice [8, 9].

The QT interval is measured from the beginning of the QRS complex to the end of the T wave and reflects the duration of ventricular depolarization and repolarization. Most of the QT interval represents ventricular repolarization. QT interval prolongation can be congenital or acquired. Congenital causes include genetic mutations leading to the loss of function affecting rectifying potassium channels in the heart's conduction system. Acquired causes of QT interval prolongation are related to cardiovascular diseases, electrolyte disturbances, and/or the provocative effect of drugs. The following drugs most frequently cause QT interval prolongation: Sotalol, Propofol, Halofantrine, Azithromycin, Clarithromycin, Erythromycin, Levofloxacin, Moxifloxacin, Thioridazine, Chlorpromazine, Amitriptyline, Fluconazole, Methadone, Domperidone, Anagrelide, Donepezil, though this effect cannot be excluded for other medications [10, 11].

Risk Assessment

The degree of QT interval prolongation is an important risk factor to consider when monitoring patients in clinical practice. Unfortunately, even modern ECG devices are not always accurate in measuring the QT interval, and the variability of measurements among specialists can be alarmingly high. Additionally, it is important to consider the heart rate (HR) as the QT interval shortens with the increased heart rate. Formulas are available to calculate the QT interval corrected for the heart rate, such as Bazett's and Fredericia's formulas [12, 13]. However, due to individual differences in the relationship between HR and the QT interval, no universal formula provides ideal correction for every patient. Gender differences are also known, with women generally having longer QT intervals than men.

Given the above, the issue of stratifying the methodology for determining the risk associated with QT interval prolongation for patient management remains relevant. It should be kept in mind that a number of factors directly affect the repolarization process, for example, cardiovascular diseases with structural and morphological changes in left ventricular hypertrophy, as well as risk factors include old age, female gender, alcoholic liver disease, atrial fibrillation, hypokalemia, hypomagnesemia, hypocalcemia, digoxin or diuretic therapy [14, 15].

In practice, significant differences remain in the administration of patients with clinically important interval prolongation [16]. If possible, it is necessary to exclude provoking drugs and minimize other risk

factors, including the correction of oxygen saturation and plasma potassium, calcium and magnesium concentrations [17]. Patients with clinically significant prolongation of the QT interval should undergo constant ECG monitoring. The QT interval on an ECG in 12 leads should be periodically evaluated, the frequency depends on the clinical picture, the circumstances, and the degree of prolongation of the QT interval [18, 19].

Polypharmacy

Over the past 20 years, there has been a significant increase in life expectancy. Consequently, the proportion of elderly and comorbid patients has risen, along with the risk of polypharmacy. Polypharmacy is defined as the simultaneous use of multiple medications [20]. While there is no universal definition regarding the number of drugs, it is generally accepted that polypharmacy involves the use of at least five drugs simultaneously. The widespread use of combination pharmacotherapy in patient treatment is often due to the presence of multiple diseases or the insufficient efficacy of monotherapy. In combined therapy, drug interactions are possible. It is known that taking two drugs leads to drug interactions in 6% of patients; taking five drugs increases the frequency of interactions to 50%. When taking ten drugs, the risk of drug interactions reaches 100%. Between 17% and 23% of drug combinations prescribed by physicians are potentially dangerous.

It is worth noting that intensive research over the past two decades has expanded our knowledge of the mechanisms and risks of QT interval prolongation induced by drug intake [21]. However, we understand that medical care technology itself is changing, with the introduction of an increasing number of medications, including those for cancer treatment during chemotherapy. There are sufficient reports, including drug instructions, on the risks of QT interval prolongation, but the safety of many drugs remains an open question. Drugs involved in QT interval prolongation cause it by blocking the rapid component of potassium channel activation, thereby prolonging the action potential.

Acquired QT Syndrome

NB! If the QT interval exceeds the 99th percentile of the QTc interval in the general population due to medication use, it is termed acquired long QT syndrome

This syndrome increases the risk of TdP tachycardia, a specific type of polymorphic ventricular tachycardia characterized by periodic fluctuations in QRS complex amplitudes on the ECG.

Congenital long QT syndrome is caused by multiple mutations in genes encoding repolarizing ion channels in cardiomyocytes; acquired long QT syndrome is associated with an increased risk of torsades de pointes (TdP) tachycardia. Torsade de pointes tachycardia occupies a special place among polymorphic ventricular tachycardia. An ECG shows a characteristic pattern with periodically increasing and decreasing QRS complexes and associated changes in the excitation propagation vector. The cause is almost always a pathological prolongation of the QT interval. This malignant arrhythmia can transform into ventricular fibrillation and thus lead to sudden cardiac death. Drug-induced prolongation of the QTc interval of more than 470 msec in men and more than 480 msec in women is called acquired drug-induced prolonged QT syndrome [22].

Nevertheless, some authors consider the QTc interval of 440 msec to be also extended [23]. There is a "gray area" between 440 msec and the upper limit values, depending on gender, which needs to be evaluated in individual clinical cases.

NB! Any prolongation of the QTc interval leads to an increased risk of ventricular tachycardia

It can be assumed that patients with a QTc of 540 msec have a 63–97% higher risk of

The risk of taking more than two QTc-prolonging medications simultaneously increases the risk of malignant arrhythmias [24], as shown in Table 1.

There are three categories of drugs that carry a risk for developing Torsades de Pointes (TdP):

1. Medications with a well-known risk of TdP: These have a well-documented risk of QT interval prolongation and TdP.

2. Medications with a possible risk of TdP: These may cause QT interval prolongation, but data on the risk of developing TdP are limited.

3. Medications with a conditional risk of TdP: These

Table 1. Drug Categories and Their QT-Prolonging Medications

Group of drugs	Name of the drug
Antiarrhythmic Drugs	Class I: Flecainide Class III: Amiodarone, Sotalol
Antiretroviral Drugs	Ritonavir, Lopinavir
Antibiotics	Macrolides: Azithromycin, Erythromycin, Clarithromycin Fluoroquinolones: Levofloxacin, Moxifloxacin, Ciprofloxacin
Antimalarial Drugs	Hydroxychloroquine, Chloroquine
Analgesics	Propofol, Methadone, Buprenorphine, Hydrocodone
Antihistamines	Hydroxyzine
Antiemetic Drugs	Ondansetron, Granisetron, Droperidol
Psychotropic Drugs	Antipsychotics: Haloperidol, Chlorpromazine Antidepressants: Doxepin, Imipramine, Clomipramine

may cause QT interval prolongation in combination with other risk factors.

NB! Risk factors for QT interval prolongation include:
> Electrolyte imbalance
> Bradycardia
> Female gender
> Acute myocardial infarction

In 2020, Tisdale et al. developed a risk score, as shown in Table 2.

Key considerations for QTc interval prolongation and risk management

It is essential to recognize that QTc interval prolongation is dose-dependent. An overdose of QTc-prolonging drugs constitutes an independent risk for malignant arrhythmias compared to therapeutic doses. The mechanism involving the activation of the cytochrome P450 3A4 (CYP3A4) system is crucial. If CYP3A4 is inhibited by concomitant use of another drug, such as erythromycin or ketoconazole, this can significantly increase the risk of QTc interval prolongation [25].

Pathophysiology of acquired long QT syndrome (LQTS) induced by drugs

The prolongation of the QT interval and the subsequent development of TdP during drug therapy are primarily due to the blockade of ion channels responsible for myocardial repolarization. On a molecular level, QTc-prolonging drugs almost always extend the action potential duration of ventricular myocardial cells by inhibiting potassium outflow during the repolarization phase [26]. A mutation in the KCNH2 gene, resulting in a loss of function of the potassium channel, also contributes to QTc prolongation in congenital LQTS type II. Risk factors such as hypokalemia, heart failure, or sinus bradycardia further exacerbate this mechanism. Cardiomyocytes are particularly sensitive to post-depolarization and medication-induced blockade of K+ channels, leading to an extended repolarization interval in the myocardium. This intensifies the gradient between the endocardium and cardiomyocytes, causing prolonged repolarization. This gradient induces varying refractory periods in the myocardium, which is critical for initiating the re-entry mechanism of TdP [27].

Table 2. Risk assessment for identifying patients at high risk of QTc interval prolongation during drug treatment

Risk Factor	Points
Age > 68 years	1
Female gender	1
Use of loop diuretics	1
Potassium ≤ 3.5 mmol/L	2
Baseline QTc ≥ 450 ms	2
Acute myocardial infarction	2
≥ 2 QTc-prolonging medications	3
Sepsis	3
Heart failure	3
1 QTc-prolonging drug	3

Note: *Low risk: ≤ 6 points, medium risk: 7–10 points, high risk: ≥ 11 points.*

How to properly measure and calculate QTc time

The American Heart Association (AHA), American College of Cardiology (ACC), and Heart Rhythm Society (HRS) have published guidelines on ECG interpretation (AHA/ACC/HRS guidelines) [6]. According to these guidelines, a normal QT interval without left bundle branch block or paced rhythm is up to 450 msec in men and up to 460 msec in women. A QTc interval exceeding 500 msec indicates a high risk for TdP [28, 29].

When measuring the QTc interval, it is crucial to adhere to three conditions:

1. Accurately determine the beginning and end of the QT interval:
   ○ The QT interval starts at the beginning of the QRS complex and ends at the end of the T wave. Proper identification is essential for accurate measurement.
2. Identify the leads best suited for QT interval measurement:
   ○ It is important to choose the leads where the QT interval can be measured most clearly and accurately. Typically, leads II, V5, or V6 are used, but this can vary depending on the patient's ECG.
3. Use appropriate formulas for wide QRS complexes:
   ○ When dealing with wide QRS complexes, use correction formulas to adjust for the impact on the QT interval. Commonly used formulas include:
   ▪ **Bazett's Formula:** $QTc = QT / \sqrt{(RR)}$
   ▪ **Fridericia's Formula:** $QTc = QT / (RR^{1/3})$
   ▪ **Other Formulas:** Hodges or Framingham formulas can also be used, depending on the clinical context and specific patient factors.

However, Bazet's formula is inaccurate for the QT interval at high heart rates. Therefore, the use of Fridericia's formula is recommended for heart rates over 90 beats per minute.

Accurate measurement and calculation of the QTc interval are fundamental for assessing the risk of QTc prolongation and associated arrhythmias, especially when patients are on medications known to affect the QT interval.

While the onset of the QRS complex is usually easily recognizable on the ECG, the end of the QT interval can vary significantly across different leads, sometimes by up to 60 msec. This variability in the QT duration is referred to as QT interval dispersion.

The QT interval should be measured in lead II or

V5. If the amplitude is too small, another lead can be used. If the T wave amplitude in leads II or V5 is less than 0.2 mV, the end of the T wave cannot be accurately determined, and another lead should be used instead. It is important to remember that the QT interval is heart rate-dependent; it may shorten with an increased heart rate and lengthen with a decreased heart rate.

Treatment of prolonged QTc interval and TdP tachycardia

Before prescribing a new medication, especially to patients already taking multiple drugs, it is crucial to evaluate the potential risk of drug interactions. For each newly prescribed medication, a risk-benefit analysis should be conducted, and the possibility of using alternative drugs that do not prolong the QTc interval should be considered.

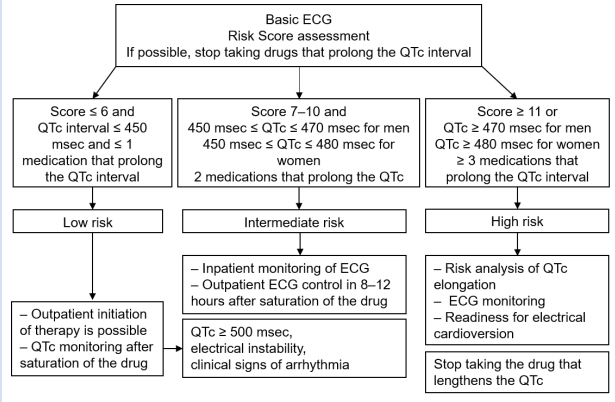
If the necessity of taking the medication is critical, a risk assessment algorithm must be employed (*Figure*).

Based on this assessment, patients can be classified into risk groups (low risk = green, intermediate risk = yellow, high risk = red):

1. Low-risk patients can be monitored and treated on an outpatient basis, with regular ECG checks.

2. Intermediate-risk patients should be hospitalized for the initiation of QTc-prolonging medication. If, after drug loading, the QTc interval does not increase beyond 500 msec or the QT interval does not increase by more than 60 msec, treatment can continue on an outpatient basis. In this case, it is recommended to monitor the ECG, especially when increasing the drug dose.

3. High-risk patients require a careful review of the indications and consideration of alternative treatment approaches. Notably, if the QTc interval exceeds 480 msec upon repeated ECG examination without any provoking factors, this indicates a diagnosis of congenital long QT syndrome, necessitating special management and treatment approaches for this patient category [10]. If the use of QTc-prolonging medications is absolutely necessary, correctable risk factors, such as electrolyte imbalances, should be addressed in the high-risk group, with continuous ECG monitoring and readiness for defibrillation [10, 30]. If a patient, regardless of their risk group, shows signs of rhythm instability after drug administration, the QTc-prolonging medications should be discontinued if possible.



The algorithm of the procedure in patients who resume taking medications that lengthen the interval

NB! Signs of electrical rhythm instability:
- Frequent ventricular extrasystoles
- Non-sustained (less than 30 seconds) paroxysms of ventricular tachycardia
- Critical prolongation of the QTc interval beyond 500 msec or an increase in the QT interval by more than 60 msec
- Syncope episodes

In case of TdP tachycardia, it is necessary to: discontinue all triggering medications; administer 2 g of intravenous magnesium sulfate, regardless of the serum Mg^{2+} level. Increasing the heart rate to ≥ 70 bpm through temporary cardiac pacing or an infusion of isoproterenol can be beneficial in preventing bradycardia or asystole pauses that cause TdP. In the presence of hypokalemia, the serum potassium level should be raised to normal levels (4.5–5 mmol/L) [31].

All patients with electrical instability should be monitored in intensive care units. In case of hemodynamic instability and persistent ventricular tachycardia, immediate electrical cardioversion is recommended, along with cardiopulmonary resuscitation in the event of cardiac arrest.

Before discharging patients with acquired long QT syndrome, they should be informed once again about the potentially life-threatening side effects of QTc-prolonging drugs. A list of such drugs or a link to the database https://www.crediblemeds.org/index.php/drugsearch should be provided to the patient before discharge.

If TdP tachycardia has been documented, family members should be screened with an ECG and a detailed history should be taken. This is necessary to diagnose clinically hidden forms of congenital long QT syndrome and to refer for genetic testing for mutations [15].

Implantable cardioverter-defibrillators (ICDs) play a critical role in the secondary prevention of sudden cardiac death (SCD), particularly in patients with prolonged QT interval who have already experienced life-threatening arrhythmias, such as ventricular fibrillation (VF) or sustained ventricular tachycardia (VT) [32–34]. ICDs are highly effective in reducing mortality in individuals at high risk for recurrent cardiac arrhythmias and have become a standard therapeutic option for secondary prevention [35].

ICDs continuously monitor heart rhythms and are designed to deliver therapy when a dangerous arrhythmia, such as VT or VF, is detected. They can deliver electrical shocks or anti-tachycardia pacing to restore a normal rhythm, preventing sudden death.

Target Population for ICDs is the patients who have survived a previous episode of VT or VF

and are at risk for recurrence or have experienced unexplained syncope with documented VT or VF and the patients with structural heart diseases like ischemic cardiomyopathy, hypertrophic cardiomyopathy, or dilated cardiomyopathy, which predispose them to arrhythmic events [36, 37].

While antiarrhythmic medications (such as amiodarone) may reduce the occurrence of arrhythmias, they have not been as effective in preventing sudden cardiac death as ICDs. Numerous studies have shown that ICDs significantly improve survival compared to drug therapy alone in high-risk populations [38].

ICDs not only act as life-saving devices but also provide long-term monitoring and protection against future arrhythmic events. They may reduce the need for repeated hospitalizations or emergency treatments related to arrhythmias [39].

Patients with ICDs may experience improved quality of life due to the sense of security provided by the device. However, there can also be psychological challenges, such as anxiety related to potential shocks or living with a device implanted. Potential complications from ICDs include inappropriate shocks, device malfunction, and infections [40]. However, the overall risk-benefit profile for patients with a history of life-threatening arrhythmias strongly favors ICD implantation.

Conclusion

• Patients taking more than 5 medications simultaneously should consult a clinical pharmacologist.

• Patients with polypharmacy are at significantly increased risk of drug-induced long QT syndrome.

• QTc-prolonging drugs vary in their risk of causing ventricular arrhythmias, so TdP risks should be assessed according to Tisdale's criteria and baseline QT interval duration on the ECG.

• Risk factors for acquired long QT syndrome include age, female gender, structural myocardial changes, electrolyte imbalances, renal failure, bradycardia, and treatment with QTc-prolonging drugs.

• Clinically, long QT syndrome manifests only in the presence of ventricular arrhythmias.

• When prescribing a potentially QTc-prolonging drug, a thorough risk-benefit assessment should be performed.

• Signs of impending TdP tachycardia after starting a QTc-prolonging drug include an increase in QTc time by more than 60 msec, absolute QTc prolongation to more than 500 msec, the occurrence of ventricular extrasystoles, and non-sustained paroxysms of ventricular tachycardia.

• In the event of TdP tachycardia, immediate discontinuation of the triggering drug, ECG monitoring in intensive care, intravenous administration of 2 g magnesium sulfate, temporary cardiac pacing, and potassium level correction are recommended.

• ICDs have become the cornerstone of secondary prevention of sudden cardiac death for patients at risk of recurrent ventricular arrhythmias, especially in case of prolonged QT interval.

Conflict of interest

V.P. Kuzmin declares no conflict of interest. I.A. Zolotovskaya declares no conflict of interest. S.P. Krivova declares no conflict of interest. R.K. Khayretdinov declares no conflict of interest. V.A. Rodionova declares no conflict of interest. O.A. Rubanenko declares no conflict of interest. I.L. Davydkin declares no conflict of interest.

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