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CLINICAL SIGNIFICANCE OF DRUG-INDUCED INTERVALS QT AND QTC PROLONGATION

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Abstract. Interval QT prolongation is a predictor of the life-threatening cardiac arrhythmias — polymorphic ventricular tachycardia (torsade de pointes). Long QT syndrome may be congenital or acquired. It is known that a wide range of both antiarrhythmic and non-cardiac medications might lead to QT interval prolongation. List of drugs that cause QT prolongation is constantly growing and being updated. The review contains current data on the clinical significance of the control of QT interval duration within drug therapy. Clinical conditions associated with an increased risk of QT interval prolongation are described. Drugs that can induce QT prolongation are also discussed.

Key words:long QT syndrome, polymorphic ventricular tachycardia, torsade de pointes, life-threatening arrhythmias.

QT interval is the time interval of the electrocardiogram (ECG) from the beginning of the Q wave to the return of the downward knee of the T wave to the isoline, reflecting the processes of depolarization and repolarization of the ventricular myocardium. The QT interval is a generally accepted and, at the same time, widely discussed indicator that reflects the electrical system of the ventricles of the heart [1–3]. It includes QRS complex (rapid depolarization and initial repolarization of the myocardium of the interventricular septum, walls of the left and right ventricles), ST segment (repolarization plateau), T wave (final repolarization). Measuring the QT interval has a large clinical impact significance mainly because its lengthening may be associated with an increased risk of death, including sudden cardiac death [2, 4–12]

due to the development of fatal ventricular arrhythmias, in particular polymorphic ventricular tachycardia

[ventricular tachycardia of the "pirouette" type - torsade de pointes, (TdP)]. Many factors contribute to the prolongation of the QT interval, among which the irrational use of medications that can prolong it deserves special attention. So, in particular, in the USA A number of antimicrobial drugs that could affect the duration of the QT interval were withdrawn from circulation [2].

QT interval assessment

Currently, there are different approaches to the interpretation of this indicator; there is no single measurement standard this interval [1, 13]. As an alternative to the QT interval, the J-T interval can be measured - an indicator characterizing only the phase (processes) of ventricular repolarization. The starting point (point J) is the transition point of the final part QRS complex into the ST segment. Theoretically (since the depolarization phase (QRS) is excluded from the process), the use of this interval is more justified [4, 13, 14]. The basis for determining QT interval prolongation is correct measurement and interpretation of the QT interval relative to heart rate values. The duration of the QT interval normally varies depending on heart rate [1]. To calculate the normal value of the QT interval taking into account heart rate, various formulas, tables and nomograms are used. V.L. Doshchitsyn first among domestic specialists drew attention to the fact that various methods for calculating the proper values of the QT interval make it difficult to actually assess it [15]. QT

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correction is carried out using various formulas: Bazett (modified), Fridericia, Framingham formula and Hodges formula [16–19]: Bazett: QTc=QT/RR0.5 (QT and RR per sec) Fridericia: QTc=QT/RR0.33 (QT and RR per second) Framingham: QTc=QT+0.154(1000–RR) (QT and RR in ms) Hodges:QTc=QT+1.75(HR–60)(QTvms,HRvudarahvmin)

Bazett's formula is primarily used for determination of the corrected QT interval in clinical studies [20].

To calculate corrected QT in atrial fibrillation atria (AF), the formula proposed by A. Sagie et al. [16]:

QTc=QT+0.154×(1000–RR) (QT and RR in ms). In addition, it is possible to use nomograms determination of prolongation of QT duration based on by comparing the QT duration and the "paired" duration of RR or heart rate [19, 21]. The main problems with measuring the QT interval include:

1) difficulties in accurately determining the beginning and end of the QT interval;

2) the difficulty of differentiating between T and U waves.

In most cases, the following standard is used: the QT interval is measured from the earliest point QRS complex to the latest point of the T wave at the point of its transition to the isoelectric T–P line. Another way is to determine the end of the T wave as the point of intersection of the isoelectric line T–P with the tangent, drawn along the maximum slope of the descending part of the T wave. The same method is used when layering to the T wave of a P or U wave. An alternative approach in such a situation is to determine the end of the tooth T as nadir - the maximum depth between the teeth.

In each lead, the QT interval and the preceding one The RR interval is measured in at least three consecutive cardiac cycles with the calculation of average values. From analysis should exclude leads with unclear differentiation of the T wave, ECG with bundle branch block and, according to some authors [22, 23], with AF, although, as mentioned earlier, you can use a special formula for calculating the QT duration. The U wave should be included into the dimension if it merges with the T wave.

Causes of QT prolongation

Prolongation of the QT interval on the surface ECG directly indicates prolongation of the action potential of at least some part of the ventricles. Dispersion of ventricular recovery time (activation time + repolarization time), repolarization asynchronism ventricles may be the basis for the re-en try mechanism and the occurrence of such serious arrhythmias as ventricular tachycardia, TdP and ventricular fibrillation [27–34]. QT prolongation may be congenital ("primary", idiopathic) and acquired ("secondary") (Table 1). A. Jervella and F. Lange-Nielsen described a syndrome including a familial form of congenital bilateral deafness, prolonged QT interval, increased incidence of syncope and sudden death. The syndrome is characterized by an autosomal recessive type of inheritance. A similar syndrome, only without congenital deafness, inherited by autosomal dominant type, described independently from each other O. Word and C. Romano [31, 35, 36]. Several genotypes are currently known congenital long QT syndrome. All of them are associated with mutations in genes encoding structural units of membrane channels of cardiomyocytes [37] (Table 1). Acquired long QT syndrome caused by various reasons: medicinal therapy, sinus bradycardia, atrioventricular block, mitral valve prolapse, brain and chest damage, atherosclerotic and post-infarction cardiosclerosis, after myo- or pericarditis, in patients who were on a low-protein diet, electrolyte imbalance (hypokalemia, hypocalcemia, hypomagnesemia) [1, 7, 27, 37, 38].

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In a study of 7,795 men and women in the Third National Health and Nutrition Survey, there were no associations were found between the length of the QT interval and such factors as drinking coffee, tea, smoking and physical activity, and alcohol consumption was associated with prolongation of the QT interval in men, but not women [39]. The duration of the QT interval may increase with taking a number of medications (Table 2): quinidine, amiodarone, procainamide, derivatives phenothiazide, barbiturates, in case of phosphorus poisoning with organic compounds, mercury, etc. [7, 19, 31, 32, 37, 40–43]. For most drugs, a direct relationship has been established between the level in blood plasma and the risk of TdP [32].

The fact that prolongation of the QT interval, including background of taking medications, is a predictor of ventricular arrhythmias, there is no doubt [2, 7, 19, 34, 37, 41, 43–46]. For example, in a study by S.M. Straus et al. [47], including more 500,000 people, over the 8-year observation period there were 775 cases of sudden death were identified, and in 320 cases Sudden death has been associated with drugs that prolong the QT interval.

Prolongation of the QT interval during antiarrhythmic therapy is associated with genetically determined decrease in the “repolarization reserve” [48] due to genetic variations, in particular, the adapter gene nitric oxide synthase protein-1 (NOS1AP) [32, 49]. High-risk patients include elderly patients, women, patients with low ejection fraction, left ventricular hypertrophy, ischemia, low Heart rate, electrolyte disturbances such as hypokalemia and hypomagnesemia, etc. (Table 3) [2, 19, 32, 41.

Since antiarrhythmic drugs are most likely to cause prolongation of the QT interval, therefore, the risk of developing TdP in the first days of starting therapy is high. Therefore, it is advisable to begin antiarrhythmic therapy in a hospital setting, when close monitoring is possible (which is especially needed in patients with structural changes in the heart), which will allow timely prevention of the development TdP or provide emergency assistance. There are studies demonstrating that in patients with supraventricular tachycardia, it is economically feasible to 72-hour observation before starting antiarrhythmic therapy [50].

Non-cardiac drugs may also cause QT prolongation and may therefore block potassium channels or interact with other drugs. This interaction may be pharmacodynamics (when both drugs block potassium channels) or pharmacokinetic (when one drug affects excretion of another, for example, by slowing down metabolism in liver due to a defect in the gene encoding cytochrome P 450, which can be considered a variant of hereditary predisposition to ventricular disorders rhythm) or mixed pharmacodynamic–pharmacokinetic [7, 19, 32, 34, 37, 42, 50, 51].

An example of a pure pharmacodynamic interaction is quinidine and sotalol, which compete for potassium channels. Interaction between cisapride and ketoconazole is an example of a pure pharmacokinetic interaction. Ketoconazole inhibits cytochrome P-4503A4, which metabolizes cisapride. As a result, it inhibits removal of the latter, which can lead to lengthening QT interval and the development of TdP.

An example of a mixed interaction is erythromycin. and cisapride. Both drugs not only block potassium channels, but erythromycin also inhibits cytochrome R-4503A4.

Among the factors predisposing to the development of TdP are hypokalemia and hypomagnesemia are especially significant and easy to correct.

It is necessary to monitor potassium and magnesium levels in patients taking medications that may affect potassium and magnesium levels magnesium, in particular diuretics. For example, Yu.M. Lopatin describes a case of the development of ventricular tachycardia against the background of

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prolongation of the QT interval to 0.8 s in a patient with previously undetected primary hyperaldosteroneism, taking indapamide.

The QT interval, corrected according to the Bazett formula, is considered to be prolonged if it lasts more than 450 in men and more than 470 ms in women, normal - less than 430 and 450, borderline - from 430 to 450 and from 450 to 470, respectively [7, 41, 45]. According to other data, a QT interval >420 ms is a predictor of sudden cardiac death [53]. A QT interval of more than 500 ms is associated with a higher risk of TdP [46–48], so it is recommended to immediately discontinue drugs that cause QT prolongation [47, 48]. Another predictor of the development of TdP is a prolongation of the QT interval by more than 500 ms. 60 ms relative to the base value.

Conclusion

Thus, by prescribing not only antiarrhythmic drugs, but also a number of other drugs, you need to remember about the possibility of increasing the risk of death of patients, taking into account the increasing likelihood of developing TdP and monitor duration of the QT interval [54].

For example, drugs that can prolongation of the QT interval is prescribed to 2.9% of critically ill patients, while the simultaneous prescription of several such drugs has been noted in 18.6% of patients [55]. According to an observational prospective study by Pickham D. et al., in acutely ill patients treated in intensive care units, prolongation of the QT interval was observed in 24% of cases, in 6% of cases it developed TdP. Predictors of prolonged QT duration were female gender, prescription of drugs that prolong the QT interval, hypokalemia, hypocalcemia, hyperglycemia, high creatinine, hypothyroidism and history of stroke [56].

When prescribing a drug that may prolong the QT interval, patients should be warned of the need to promptly report to your doctor any symptoms that may be manifestations of TdP: fainting, paroxysmal, especially newly developed, palpitations and pre-syncope, pre-syncope without heartbeat, as well as in intercurrent conditions or treatments that may lead to hypokalemia (for example, gastroenteritis or the addition of diuretics). Regular electrocardiographic examination is necessary to detect asymptomatic prolongation of the QT interval >500 ms. When determining the duration of the QT interval, it is advisable to follow the following rules:

1. Measurements should be taken: manually by ECG in 12 leads; the distance from the beginning of the QRS complex to the end of the QT interval should be measured; averaging over 3–5 complexes in one lead is necessary;

2. The U wave should be included in the measurement if it merges with the T wave;

3. The QT interval should be assessed at its peak concentrations in the blood plasma of a substance capable of cause QT prolongation;

4. The QT interval should be adjusted taking into account heart rate.

In case of prolongation of the QT interval, it is advisable reconsider the treatment strategy by choosing an alternative pharmacotherapy, monitor drug interactions that can worsen the prognosis, bradycardia and electrolyte disturbances [47, 48]. Electronic resources are available (eg http://www.azcert.org/index.cfm), allowing you to get list of drugs that can lead to an increase in QT duration, information on the effect of drugs drugs on the duration of the QT interval, and also assess the risk of drug interactions.

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