

Drug-Induced QT Interval Prolongation

Domina Petric, MD*

University Hospital Center, Clinical Pharmacology and Toxicology
Soltanska 1, 21 000 Split, Croatia.

*Correspondence:

Domina Petric, University Hospital Center, Clinical pharmacology and toxicology, Soltanska 1, 21 000 Split, Croatia, Tel: +385955820879.

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ABSTRACT

The correct measurement of the QT interval (using the QT correction formulas, preferably Fridericia and Framingham) as well as a correct interpretation of the causes and of the clinical consequences of a QT prolongation is very important in clinical practice. Drug-induced long QT syndrome (DILQTS) is one of the most common causes of LQTS. In the diagnosis and management of the DILQTS, it can be useful to follow the three-step rule presented in this article: detailed pharmacological anamnesis and correct ECG interpretation; database search and clinical interpretation; confirmatory test.

Keywords

DILQTS, Pharmacology, QTc.

Introduction

The correct measurement of the QT interval as well as a correct interpretation of the causes and of the clinical consequences of a QT prolongation is very important in clinical practice. Many factors can cause the prolongation of the QT interval, including drugs, electrolyte imbalances, hormonal influence, and comorbidities [1]. Drug safety precautions recommend monitoring of the corrected QT interval (QTc). A study showed that Fridericia and Framingham correction formulae showed the best rate correction and significantly improved prediction of 30-day and 1-year mortality, whilst Bazett formula overestimated the number of patients with potentially dangerous QTc prolongation, which could lead to unnecessary safety measurements as withholding the patient of first-choice medication [2]. Background QTc-interval prolongation has been associated with serious adverse events, such as Torsade de Pointes and sudden cardiac death [3].

Risk Factors for Drug-Induced QT Interval Prolongation

Concomitant risk factors predisposing patients to long QT syndrome and consequently development of Torsades de Pointes with QT prolonging drugs are female sex, advanced age, recent conversion from atrial fibrillation with QT prolonging drugs, concurrent use of more than one QT prolonging drug, electrolyte

disturbance (hypokalemia, hypomagnesemia, hypocalcemia), use of diuretics, hepatic and renal dysfunction, bradycardia, occult congenital long QT syndrome or silent mutations in LQTS genes, ion-channel polymorphism, underlying heart disease such as heart failure (because of down-regulation of K channels and up-regulation of Ca channels), left ventricular hypertrophy and myocardial infarction, baseline QT prolongation, rapid rate of intravenous infusion with a QT prolonging drug, high drug concentration and digitalis therapy [4].

Results of a cross-sectional study carried out during one-year period in coronary care units of two major tertiary care hospitals of Khyber Pakhtunkhwa, Pakistan showed that most frequent QT prolonging risk factors included use of ≥ 1 QT prolonging drugs (74.9%) and myocardial infarction (61.3%). Other risk factors were female gender, hypertension, diabetes mellitus, old age, coronary artery disease, acute coronary syndrome, cardiomyopathy, ischemic heart disease, atrial fibrillation, left ventricular failure, complete heart block, stroke, congestive heart failure, left bundle branch block, bradycardia, and electrolyte imbalance [5].

In most cases, QT prolongation is caused by factors that prolong the duration of the action potential, mainly by delaying the repolarization phase 3. For example, left ventricular hypertrophy generates a significant electrical remodeling and its most characteristic feature is an extension of the duration of ventricular

action potentials. This remodeling is not homogeneous and therefore also increases the dispersion of repolarization and hence favors the occurrence of polymorphic ventricular tachycardia and sudden death. The exact molecular mechanism of drug induced QT prolongation is partially known. There are two well described mechanisms: blocking of the ion channel cavity of hERG (the human Ether-à-go-go-Related Gene); or causing an abnormal protein trafficking required for the location of hERG subunits in cell membrane. Drugs can prolong the QT interval by one of the cited mechanisms or through both simultaneously (fluoxetine). All of them cause the IKr (delayed rectifier potassium current) impairment [6].

To conclude, risk factors for the development of drug-induced long QT syndrome (DILQTS) are numerous: female sex, advanced age, atrial fibrillation and recent conversion from atrial fibrillation with QT prolonging drugs, concurrent use of more than one QT prolonging drug (one of the most common causes), electrolyte disturbance (hypokalemia, hypomagnesemia, hypocalcemia), history of myocardial infarction, coronary artery disease, diabetes mellitus, cardiomyopathy, ischemic heart disease, LBBB, bradycardia, left ventricular failure, congestive heart failure, complete heart block, history of stroke, occult congenital long QT syndrome or silent mutations in LQTS genes, ion-channel polymorphism, hepatic and renal dysfunction.

Diagnosis and Management of DILQTS

First step in the diagnosis and management of DILQTS is to properly analyze ECG with special reference to QT interval and QTc calculation using one of the available formulas (preferably Fridericia and Framingham correction formulae). If QTc is prolonged, it is very important to take a detailed history, with special reference to detailed pharmacological anamnesis.

Second step is to search the database and to identify one or more drugs that could be the cause of QT-prolongation.

One of the most useful databases for this problem is CredibleMeds [7].

Each QT prolonging drug in CredibleMeds database is assigned one of the below listed categories based on the risk for the induction of Torsades de Pointes (TdP):

1. Known Risk of TdP: These drugs prolong the QT interval and are clearly associated with a known risk of TdP, even when taken as recommended.

2. Possible Risk of TdP: These drugs can cause QT interval prolongation, but currently lack evidence for a risk of TdP when taken as recommended.

3. Conditional Risk of TdP: these drugs are associated with TdP, but only under certain conditions of their use (excessive dose, in patients with conditions such as hypokalemia, or when taken with interacting drugs) or by creating conditions that facilitate or induce TdP (by inhibiting metabolism of a QT-prolonging drug or by causing an electrolyte disturbance that induced TdP).

4. Drugs to Avoid in Congenital Long QT Syndrome (cLQTS):

these drugs pose a high risk of TdP for patients with cLQTS and include all those in the above three categories (KR, PR, CR) plus additional drugs that do not prolong the QT interval per se, but which have a Special Risk because of their other actions.

If one or more drugs fall into the known risk category, then the alternative drug must be considered. If there is no alternative drug, and the benefit of taking the drug with known risk is higher than the risk for TdP development, then this patient must be frequently monitored (with regular QTc interval controls) and all risk factors that could worsen DILQTS must be managed if possible (for example, electrolyte imbalance must be corrected).

If one or more drugs fall into the possible or conditional risk category, then all of the risk factors that can co-induce or worsen DILQTS must be managed if possible. Patient must be frequently monitored and the benefit/risk ratio must be frequently re-evaluated.

Patients with cLQTS must be referred to both cardiologist (cardiac electrophysiologist) and pharmacologist in order to find individualized pharmacotherapy with the lowest possible risk for TdP development.

Third step is required when a suspect drug is replaced with an alternative drug, and when the confirmation is wanted, and includes the following: calculation of five drug elimination half-lives (drug elimination half-life is multiplied with 5; during this time more than 96% of the drug is eliminated from the bloodstream) and recording a new ECG after the five half-lives have passed. If QTc interval is normal after the discontinuation of the suspect drug (after five half-lives), then the suspect drug is confirmed as a cause of DILQTS. If this confirmatory test is positive, then it is very important to report the side effect to national and/or international adverse drug reactions reporting systems.

Important Drug-Drug Interactions

It is also important to check if there is clinically relevant interaction between two QT-interval prolonging drugs. Synergistic effect on QT-prolongation can increase the risk for the development of TdP.

There are numerous examples of clinically relevant QT-interval prolonging drug-drug interactions, some of which are listed below:

- Amiodarone and Quinolones: the interaction is associated with an increased risk of TdP and/or QTc prolongation on ECG by concomitant blockade of cardiac potassium channels [7].
- Concurrent use of escitalopram with amiodarone may result with an increased risk for QT interval prolongation.
- Concurrent use of fluconazole with ziprasidone may result with an increased risk for QT interval prolongation [8].

Conclusion

The correct measurement of the QT interval (using the QT correction formulas, preferably Fridericia and Framingham) as well as a correct interpretation of the causes and of the clinical

consequences of a QT prolongation is very important in clinical practice. DILQTS is one of the most common causes of LQTS. In the diagnosis and management of the DILQTS, it can be useful to follow the three- step rule presented in this article: detailed pharmacological anamnesis and correct ECG interpretation with special reference to QTc; database search and clinical interpretation; confirmatory test.

It is also important to diagnose and manage additional risk factors (if possible) such as electrolyte disturbance (hypokalemia, hypomagnesemia, hypocalcemia), history of myocardial infarction, coronary artery disease, diabetes mellitus, cardiomyopathy, ischemic heart disease, LBBB, bradycardia, left ventricular failure, congestive heart failure, complete heart block, history of stroke, occult congenital long QT syndrome or silent mutations in LQTS genes, ion- channel polymorphism, hepatic and renal dysfunction.

It is also important to check all clinically relevant drug-drug interactions because synergistic effect of two QT interval prolonging drugs can increase the risk of cardiac adverse effects (Torsade de Pointes, sudden cardiac death).

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