

## Drug-Induced QT Interval Prolongation and Torsade De Pointes: Identification of Risk Factors

### *İlaça Bağlı QT İnterval Uzaması ve Torsade De Pointes: Risk Faktörlerinin Saptanması*

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A progressively increasing number of non-cardiac agents prolong cardiac repolarization predisposing to polymorphic ventricular tachycardia, termed torsade de pointes (TdP), and sudden cardiac death. Drug-induced QT interval prolongation is considered the most frequent cause of withdrawal or relabeling of marketed drugs. Although the exact mechanisms are incompletely understood, the majority of these agents exhibit direct electrophysiological effects on the rapidly activating delayed rectifier potassium current. Additionally, pharmacokinetic interactions with drugs known to inhibit cytochrome P450 isoenzymes may enhance the torsadogenic potential of these agents. Genetic analyses have identified the subclinical congenital form in 5-10% of patients with drug-induced long QT syndrome. The likelihood of drug-induced long QT syndrome is difficult to be predicted in routine clinical practice. However, clinical history may reveal well-established risk factors that act as "effect amplifiers" making an otherwise relatively safe drug dangerous with regard to risk for TdP. The current review describes the underlying mechanisms of drug-induced QT interval prolongation and TdP as well as the risk factors that predispose to this potentially life-threatening conditions.

**Key words:** Drugs; long QT interval; torsade de pointes; sudden cardiac death.

Kardiyoloji alanı dışında kullanılmakta olan önemli sayıda ilaç, Torsade de pointes (TdP), olarak isimlendirilen, polimorfik ventrikül taşikardisine ve ani kardiyak ölüme zemin hazırlayan kardiyak repolarizasyonu uzatmaktadır. Piyasadaki ilaçların toplatılmasının ya da yeniden sürülmesinin en sık nedeninin ilaca bağlı QT interval uzaması olduğu görülmektedir. Tam işleyişleri bütünüyle anlaşılmasına rağmen, bu ilaçların çoğunluğu gecikmiş düzenleyici potasyum akımını hızlıca etkinleştirerek doğrudan elektrofizyolojik etkiler gösterir. Ek olarak, sitokrom P450 isoenzimlerini baskıladığı bilinen ilaçlar ile farmakokinetik etkileşimleri bu ilaçların proaritmik etkilerini artırabilir. Genetik analizler, ilaca bağlı uzun QT sendromlu hastaların %5-10'unda doğuştan subklinik form ortaya koymuştur. İlaça bağlı uzun QT sendromu ihtimalinin rutin klinik uygulamada tahmin edilmesi zordur. Ancak, klinik öykü, normalde TdP riski açısından oldukça güvenli bir ilacı tehlikeli hale sokan "etki yükseltici" olarak rol oynayan iyi belirlenmiş risk faktörlerini açığa çıkarabilir. Bu derlemede ilaca bağlı QT uzaması ve TdP mekanizmaları ve yaşamı tehdit eden durumlara zemin hazırlayan risk faktörleri ele alınmaktadır.

**Anahtar sözcükler:** İlaçlar; uzun QT aralığı; torsade de pointes; ani kardiyak ölüm.

A continuously rising number of non-antiarrhythmic agents have been shown to prolong cardiac repolarization predisposing to a certain type of polymorphic ventricular tachycardia termed torsade de pointes (TdP) and sudden cardiac death.<sup>[1-5]</sup> Drug-induced QT interval prolongation is considered the most frequent cause of withdrawal or relabeling of marketed drugs in the last decade, but this adverse drug reaction is assumed to be rare (less than one in 100 000).<sup>[5]</sup> Drugs with proven lengthening of the QT interval or a definite association with TdP are common and are estimated to compose approximately 2-3% of all prescriptions written.<sup>[6]</sup> Antibiotics and psychotropic drugs are the most common non-cardiac drugs involved in drug-induced QT interval prolongation, which in the vast majority of cases are prescribed by non-cardiologists.<sup>[1,5,7]</sup> Drugs implicated in QT interval prolongation and TdP are listed in Table 1.

The prescription of non-cardiac QT-prolonging agents has been recently associated with a significantly increased risk of sudden cardiac death in the general population. The risk of death has been showed to be higher in women and in recent starters.<sup>[8]</sup> However, the likelihood of drug-induced TdP is difficult to be predicted in routine clinical practice. The present review describes the underlying mechanisms of drug-induced QT interval prolongation and TdP as well as the risk factors that predispose to this potentially life-threatening condition.

### ECG MARKERS OF VENTRICULAR REPOLARIZATION

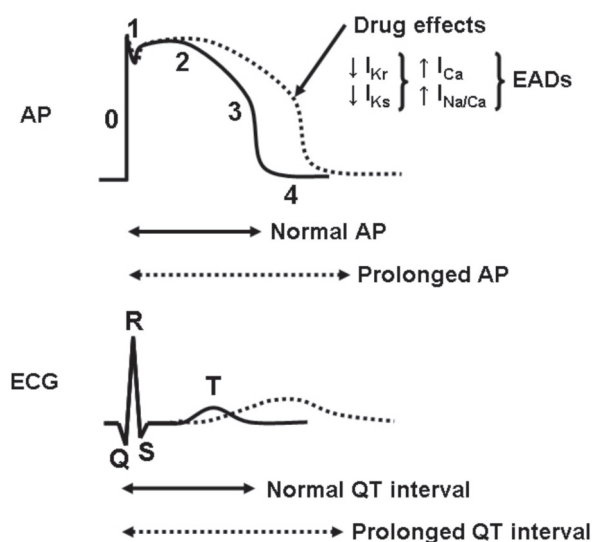
The QT interval is considered as the ECG index of ventricular repolarization. Correct measurement of the QT interval is of paramount importance for the diagnosis of drug-induced QT interval prolongation. Most physicians, including many cardiologists, cannot recognize a long QT interval. Viskin et al.<sup>[9]</sup> have shown that correct classification of the QT interval as either "long" or "normal" was achieved by 96% of QT experts and 62% of arrhythmia experts, but by less than 25% of cardiologists and non-cardiologists. The QT interval is measured from the beginning of the QRS complex to the end of the T wave on the surface electrocardiogram (ECG). Despite the fact that there are no sufficient data regarding which lead or leads to use for QT interval measurement, lead II is considered the appropriate one because the vectors of repolarization result in a long single wave rather than discrete T and U waves.<sup>[10]</sup> The QT interval is influenced by the heart rate. Rate acceleration normally leads to QT shortening, whereas bradycardia leads to QT lengthening.<sup>[11]</sup> The RR interval preceding the QT interval should be measured for rate correction.<sup>[11,12]</sup> Several formulas may be used to correct the QT interval (QTc). The most commonly used formulas are Fridericia's cube root formula ( $QTc = QT / RR^{1/3}$ ) and Bazett's square root formula ( $QTc = QT / RR^{1/2}$ ). Fridericia's equation is preferred at extremes of physiological heart rate.<sup>[11,12]</sup> Apart from heart rate, the duration of the

**Table 1. Drugs implicated in drug-induced QT interval prolongation and TdP**

Category	Drugs
Antiarrhythmics	Disopyramide, procainamide, quinidine, mexiletine, propafenone, flecainide, d, l-sotalol, amiodarone, bretylium, dofetilide, ibutilide, azimilide, ajmaline
Antimicrobials	Erythromycin, clarithromycin, azithromycin, levofloxacin, moxifloxacin, sparfloxacin, gatifloxacin, grepafloxacin, trimethoprim-sulfamethoxazole, pentamidine, quinine, itraconazole, ketoconazole, fluconazole, chloroquine, halofantrine, mefloquine, amantadine, spiramycin
Antihistamines	Astemizole, diphenhydramine, ebastine, terfenadine, hydroxyzine
Antidepressants	Doxepin, venlafaxine, fluoxetine, desipramine, imipramine, clomipramine, paroxetine, sertraline, citalopram
Antipsychotics	Chlorpromazine, prochlorperazine, trifluoperazine, haloperidol, fluphenazine, felbamate, thioridazine, droperidol, pimozide, mesoridazine, risperidone, quetiapine, ziprasidone, lithium, chloral hydrate, pericycline, sertindole, sultopride, zimeldine, maprotiline
Diuretics	Indapamide, thiazide, furosemide
Gastrointestinal stimulants	Cisapride, metoclopramide, domperdone
Others	Albuterol, salmeterol, arsenic trioxide, aconitine, veratridine, vincamine, terodiline, tacrolimus budipine, tizanidine tiapride, cocaine, organophosphorus compounds

QT interval is also influenced by sympathovagal activity, drugs, genetic abnormalities, electrolyte disorders, cardiac or metabolic diseases and changes of cardiac afterload.<sup>[12]</sup>

QTc values greater than 450 msec in men and 470 msec in women are considered abnormal. Values ranging between 430-450 msec in men and 450-470 msec in women are considered borderline.<sup>[12]</sup> The QTc interval is the best available predictor of TdP episodes.<sup>[13]</sup> The majority of drug-induced TdP occur with QTc values of more than 500 msec.<sup>[14]</sup> Data from patients with congenital long QT syndrome (LQTS) have shown that a QTc interval greater than 500 msec is related to an increased risk for arrhythmic events.<sup>[15]</sup> However, there is no established threshold below which prolongation of the QTc interval is considered free of proarrhythmic events. In terms of QTc change from baseline on treatment, it has been recommended



**Fig. 1.** Relationship between the phases of ventricular transmembrane action potential (AP) and the surface electrocardiogram (ECG). A reduction of outward currents ( $I_{Kr}$ ,  $I_{Ks}$ ) during phase 2 and 3 of the AP leads to QT interval prolongation. Activation of inward depolarizing currents ( $I_{Ca}$ ,  $I_{Na/Ca}$ ) may then give rise to early afterdepolarizations (EADs).

that an increase of 30 ms is a potential cause for concern and that a 60 ms increase is a definite cause for concern.<sup>[16]</sup> Additionally, QT dispersion (defined as the difference between the maximum and minimum QT interval of the 12-leads) greater than 100 ms is considered abnormal.<sup>[16]</sup>

New ECG markers of ventricular repolarization including the Tpeak-end interval and the Tpeak-end/QT ratio are still under investigation. The Tpeak-end interval in precordial leads is considered as an index of transmural dispersion of repolarization, while the Tp-e interval measured in limb leads is more likely to reflect global dispersion, including apico-basal and inter-ventricular dispersion of repolarization.<sup>[17]</sup> The Tpeak-end interval has been reported to be prolonged in congenital LQTS and to predict TdP in acquired LQTS.<sup>[18]</sup> Yamaguchi et al.<sup>[19]</sup> have demonstrated that the Tpeak-end/QT ratio is a better predictor of TdP as compared to QTc interval and QT dispersion in patients with acquired LQTS. In their study, Tpeak-end/QT ratio greater than 0.28 was strongly associated with risk of developing TdP.<sup>[19]</sup>

### MECHANISMS OF DRUG-INDUCED QT INTERVAL PROLONGATION AND TORSADE DE POINTES

At a cellular level, the repolarisation phase is driven predominantly by the outward movement of potassium ions. Two important potassium currents participating in ventricular repolarisation are the components of the delayed rectifier current,  $I_{Kr}$  (rapid) and  $I_{Ks}$  (slow). The majority of non-cardiac QT-prolonging agents exhibit direct electrophysiological effects on the rapidly activating delayed rectifier  $I_{Kr}$  cur-

rent encoded by the human ether-a-go-go-related gene (HERG, now termed  $KCNH2$ ).<sup>[1,5]</sup> However, many drugs block multiple cardiac ion channels ( $I_{Kr}$ ,  $I_{Ks}$ ,  $I_{Na}$ ) leading to a more complex shift of action potential morphology.<sup>[1,5]</sup> As showed in Figure 1,  $I_{Kr}$  blockade leads to a delay in phase 3 of repolarization of the action potential (reflected as QT interval prolongation on surface ECG). Activation of inward depolarizing currents (most likely L-type calcium channels or sodium-calcium exchange current) may then give rise to early afterdepolarizations that appear as depolarizing oscillations in membrane voltage during phases 2 and 3 of the action potential.<sup>[20-22]</sup> Early afterdepolarizations that reach the threshold voltage cause ventricular extrasystoles. These phenomena are more readily induced in the His-Purkinje network and also in M cells from the mid ventricular myocardium.<sup>[20-22]</sup> Compared to subendocardial or subepicardial cells, M cells show much more pronounced action potential prolongation in response to  $I_{Kr}$  blockade.<sup>[20-22]</sup> The resultant heterogeneity in ventricular repolarization creates a zone of functional refractoriness in the mid myocardial layer, which is probably the basis of the re-entry that is sustaining the TdP.<sup>[20-22]</sup> A "short-long-short" sequence (an extrasystole, followed by a post-extrasystolic pause) precedes the onset of TdP in most cases.<sup>[23]</sup> An example of a self-terminated episode of TdP preceded by the characteristic "short-long-short" sequence in a patient with drug-induced QT interval prolongation is shown in Figure 2.

Furthermore, pharmacokinetic interactions with drugs known to inhibit cytochrome P450 isoenzymes (CYP3A4 or CYP2D6) enhance the torsadogenic potential of these agents by decreasing their clearance.<sup>[1,5,20]</sup> CYP3A4 activity can be inhibited by a wide variety of drugs including some macrolide antibiotics, ketoconazole and related antifungals, cimetidine, fluoxetine, protease inhibitors, and amiodarone. In addition, many non-drug factors, including age, smoking, hepatic disease, genetic polymorphisms and grapefruit juice may lead to CYP3A4 inhibition.<sup>[7]</sup> Finally,



**Fig. 2.** Example of a self-terminated episode of TdP preceded by the characteristic "short-long-short" sequence in a patient with drug-induced QT interval prolongation.



**Table 2. Risk factors for drug-induced QT interval prolongation and TdP**

Risk factors
Female sex
Advanced age
Electrolyte imbalances (hypokalemia, hypomagnesemia, hypocalcemia)
Bradycardia
Congestive heart failure
Cardiomyopathies
Cardiac hypertrophy
Anorexia nervosa, starvation
Hypothermia
Hypothyroidism
Renal and liver insufficiency
Cytochrome P450 isoenzyme CYP3A4 inhibitors
Baseline QT interval prolongation
Ion channel mutations/polymorphisms
Polypharmacy

cytochrome P450 CYP2D6 is functionally absent in approximately 7% of white and black individuals (poor metabolizer group) because of loss of function gene variants.<sup>[24]</sup>

## RISK FACTORS FOR DRUG-INDUCED QT INTERVAL PROLONGATION AND TDP

The susceptibility of drug-induced QT interval prolongation varies significantly among individuals. The unifying concept of “reduced cardiac repolarization reserve” has been proposed to explain the mechanism by which some patients are rendered more susceptible than others to the QT-prolonging effects of drugs.<sup>[5,20,21]</sup> Silent mutations and/or polymorphisms in genes encoding cardiac ion channels leading to a reduced cardiac repolarization reserve hold the key to understanding why healthy individuals will be exposed to risk for LQTS when taking medication for unrelated causes.<sup>[5,20,21,25,26]</sup> Genetic analyses have identified the subclinical congenital form in 5-10% of patients with drug-induced LQTS.<sup>[26]</sup> Mutations have been reported in *KCNQ1*, *KCNH2*, *KCNE1*, *KCNE2* and *SCN5A* genes.<sup>[5,20,21,25,26]</sup> Therefore, the administration of an  $I_{Kr}$  current blocking agent may significantly prolong the QT interval in these silent carriers predisposing them to TdP and sudden cardiac death.

The likelihood of drug-induced LQTS is difficult to be predicted in routine clinical practice. However, clinical history may reveal well-established risk factors that act as “effect amplifiers” making an otherwise relatively safe drug dangerous with regard to risk for TdP (Table 2). These risk factors include female gender, cardiac hypertrophy, chronic heart failure, cardiomyopathies, bradycardia, electrolyte imbalance (hypokalemia, hypomagnesemia, hypocalcemia), digitalis therapy, hypothermia, and hypothyroidism.

<sup>[1,5,7,11,12,20,21]</sup> The vast majority of patients with drug-induced TdP display at least one of these risk factors. In a recent study including 21 patients with drug-induced QT interval prolongation, advanced age (>60 years), female gender, hypertension and paroxysmal atrial tachyarrhythmias were the most common identifiable pre-existing risk factors. In this study, TdP and cardiac arrest events were significantly associated with a QTc interval >510 ms.<sup>[27]</sup> It has been estimated that approximately 70% of cases of drug-induced TdP occur in females.<sup>[28]</sup> A reduced cardiac repolarization reserve closely related to sex steroids has been proposed to explain the increased propensity of women to develop drug-induced TdP.<sup>[27]</sup> Testosterone, by increasing  $I_{Kr}$  and  $I_{Kur}$  currents, shortens the QT interval and reduces the risk of TdP in males.<sup>[29]</sup> Polypharmacy should also be considered as a risk factor for drug-induced LQTS. We have recently shown that potential drug-interactions involving inhibition of cytochrome P450 isoenzymes were considered responsible in 24% of cases.<sup>[27]</sup> An analysis of medication lists from 1.1 million patients have shown that 22.8% were taking at least one medication with potential for QT prolongation, 9.4% were taking two such medications, and 0.7% were taking three or more QT-prolonging drugs. Psychotropic drugs were involved in 50% of cases.<sup>[30]</sup>

## TREATMENT

The management of drug-induced TdP requires the identification and withdrawal of the suspicious medication. Administration of intravenous magnesium sulfate (2 g bolus followed by an infusion of 2-4 mg/minute) is the treatment of choice regardless of serum level.<sup>[20,31]</sup> Similarly, correction of potassium concentration (4.5-5 mmol/l) is considered important.<sup>[20]</sup> In cases of hemodynamically unstable polymorphic ventricular tachycardia, immediate non-synchronized defibrillation is indicated.<sup>[20]</sup> Temporary pacing is indicated in cases refractory to magnesium sulfate or when TdP is precipitated by a pause or bradycardia.<sup>[32]</sup> Pacing (90-110 beats/min) is highly effective in preventing recurrences.<sup>[20,32]</sup> Intravenous administration of isoproterenol may be useful if temporary pacing is unavailable.<sup>[33]</sup>

## CONCLUSION

Drug-induced LQTS should always be considered as a predictor of sudden cardiac, and thus should prompt critical reevaluation of the risks and benefits of the suspicious medication. In clinical practice, adverse effects of QT-prolonging drugs can be prevented by not exceeding the recommended dose; by restricting the dose in patients with pre-existing risk factors; and by avoiding concomitant administration of agents that inhibit the metabolism of known drugs that prolong the QT interval. Survivors of drug-induced TdP and family members of drug-induced TdP fatalities require careful examination and possibly genetic testing for the presence of congenital LQTS-associated channelopathy.

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