

Review Article

Drug-Induced Long QT Syndrome

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A continuously growing number of non-antiarrhythmic agents have been shown to prolong cardiac repolarisation, predisposing to a certain type of polymorphic ventricular tachycardia termed torsades de pointes (TdP) and sudden cardiac death.¹⁻⁵ Drug-induced long QT syndrome (LQTS) is considered the most frequent cause of withdrawal or relabelling of marketed drugs in the last decade.⁵ Drugs with proven lengthening of the QT interval or a definite association with TdP are common and are estimated to comprise approximately 2-3% of all prescriptions written.⁶ As shown in Table 1, antibiotics and psychotropic drugs are the most common non-cardiac drugs involved in drug-induced LQTS and, in the vast majority of cases, are prescribed by non-cardiologists.^{1,5,7} This list can be accessed via the internet:

- www.torsades.org
- www.qt drugs.org
- www.longqt.org
- www.sads.org

The prescription of non-cardiac QT-prolonging agents has recently been associated with a significantly increased risk of sudden cardiac death in the general population. The risk of death has been shown to be higher in women and in recent starters.⁸ However, the likelihood of drug-induced TdP is difficult to predict in routine clinical practice. The present brief review highlights the mechanisms underlying

ing drug-induced LQTS, as well as the identification of easily recognised risk factors that predispose to this potentially life-threatening condition.

Measurement of the QT interval

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 insufficient data regarding which lead or leads to use for QT interval measurement, lead II is considered the appropriate one because the vectors of repolarisation result in a long single wave rather than discrete T and U waves.⁹ The QT interval is influenced by the heart rate. Rate acceleration normally leads to QT shortening, whereas bradycardia leads to QT lengthening.¹⁰ The RR interval preceding the QT interval should be measured for rate correction.^{10,11} Several formulae may be used to correct the QT interval (QTc). The most commonly used formulae 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.^{10,11} Apart from heart rate, the duration of the QT interval is also influenced by sympathovagal activity, drugs, genetic abnormalities, electrolyte disorders, cardiac or metabolic diseases and changes of cardiac afterload.¹¹

Table 1. Drugs implicated in drug-induced long QT syndrome.

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, fluphenazine, felbamate, haloperidol, thioridazine, droperidol, mesoridazine, pimozide, risperidone, quetiapine, ziprasidone, lithium, chloral hydrate, pericycline, sertindole, sultopride, zimeldine, maprotiline
Anti-migraine	Naratriptan, sumatriptan, zolmitriptan
Bronchodilators	Albuterol, salmeterol
Diuretics	Indapamide, thiazide, furosemide
Gastrointestinal stimulants	Cisapride, metoclopramide, domperidone
Hormones	Octreotide, vasopressin
Immunosuppressives	Tacrolimus
Others	Arsenic trioxide, aconitine, veratridine, vincamine, terodiline, budipine, tizanidine, tiapride, cocaine, organophosphorus compounds

QTc values greater than 450 ms in men and 470 ms in women are considered abnormal. Values ranging between 430-450 ms in men and 450-470 ms in women are considered borderline.¹¹ The QTc interval is the best available predictor of TdP episodes.¹² The majority of drug-induced TdP occur with QTc values of more than 500 ms.¹³ Data from patients with congenital LQTS have shown that a QTc interval greater than 500 ms is associated with an increased risk for arrhythmic events.¹⁴ However, there is no established threshold below which prolongation of the QTc interval is considered free of proarrhythmic events.

Mechanisms of drug-induced arrhythmia

The majority of non-cardiac QT-prolonging agents exhibit direct electrophysiological effects on the rapidly activating delayed rectifier (repolarising) potassium current (I_{Kr}) encoded by the human ether-a-go-go-related gene (*HERG*, now termed *KCNH2*).^{1,5} As shown in Figure 1, I_{Kr} blockade leads to a delay in phase 3 of repolarisation of the action potential (reflected as QT interval prolongation on the surface ECG). Activation of inward depolarising currents (most likely L-type calcium channels or sodium-calcium exchange current) may then give rise to early afterdepolarisations that appear as depolaris-

ing oscillations in membrane voltage during phases 2 and 3 of the action potential.¹⁵⁻¹⁷ Early afterdepolarisations 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.¹⁵⁻¹⁷ Compared to subendocardial or subepicardial cells, M cells show a much more pronounced action potential prolongation in response to I_{Kr} blockade.¹⁵⁻¹⁷ The resultant heterogeneity in ventricular repolarisation creates a zone of functional refractoriness in the mid myocardial layer, which is probably the basis of the re-entry that sustains the TdP.¹⁵⁻¹⁷ Many drugs block multiple cardiac ion channels (I_{Kr} , I_{Ks} , I_{Na}) leading to a more complex shift of action potential morphology.^{1,5}

Furthermore, pharmacokinetic interactions with drugs known to inhibit cytochrome P450 isoenzymes (mainly CYP3A4) enhance the torsadogenic potential of these agents by decreasing their clearance.^{1,5,15} 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.⁷

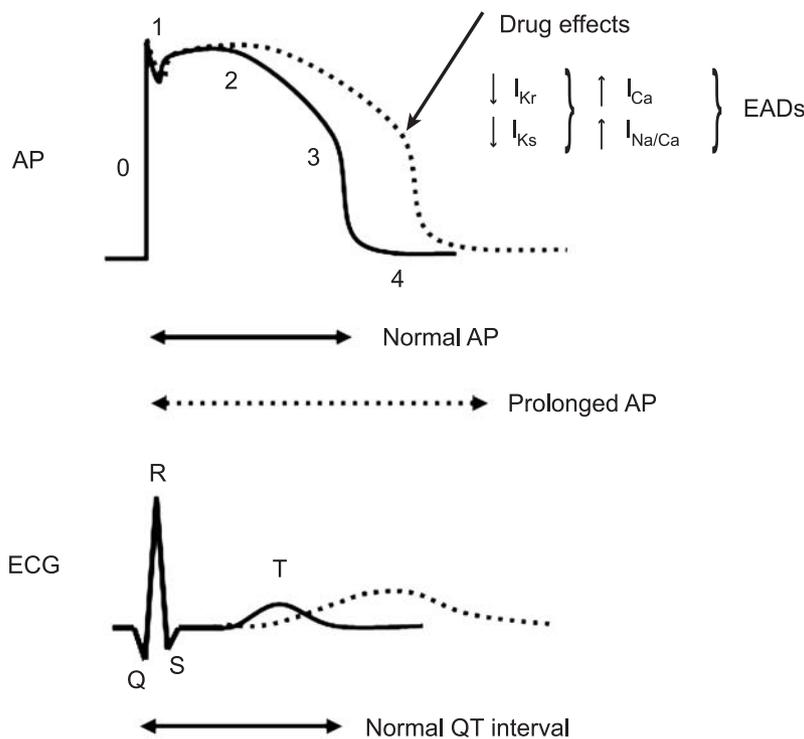


Figure 1. Relationship between the phases of ventricular transmembrane action potential (AP) and the surface electrocardiogram (ECG). A reduction of outward currents (I_{Kr} , I_{Ks}) during phases 2 and 3 of the AP leads to QT interval prolongation. Activation of inward depolarising currents (I_{Ca}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

Risk factors for drug-induced long QT syndrome

The susceptibility to drug-induced LQTS varies significantly among individuals. The unifying concept of “reduced cardiac repolarisation 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.^{5,15,16} Silent mutations and/or polymorphisms in genes encoding cardiac ion channels leading to a reduced cardiac repolarisation reserve hold the key to understanding why healthy individuals will be exposed to risk for LQTS when taking medication for unrelated causes.^{5,15,16,18-20} Genetic analyses have identified the subclinical congenital form in 5-10% of patients with drug-induced LQTS.¹⁹ Mutations have been reported in *KCNQ1*, *KCNH2*, *KCNE1*, *KCNE2* and *SCN5A* genes.^{5,15,16,18-20} 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 predict 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, car-

Table 2. Risk factors for drug-induced long QT syndrome.

Risk factors
Female sex
Advanced age
Electrolyte imbalances (hypokalaemia, hypomagnesaemia, hypocalcaemia)
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

diomyopathies, bradycardia, electrolyte imbalance (hypokalaemia, hypomagnesaemia, hypocalcaemia), digitalis therapy, hypothermia, and hypothyroidism.^{1,5,7,10,11,15,16} The vast majority of patients with drug-induced TdP display at least one of these risk factors. It has been estimated that approximately 70% of cases of drug-induced TdP occur in females.²¹ A reduced cardiac repolarisation reserve closely related to sex steroids has been proposed to explain the increased propensity of women to develop drug-in-

duced TdP.²¹ Testosterone, by increasing I_{Kr} and I_{Kur} currents, shortens the QT interval and reduces the risk of TdP in males.²² Polypharmacy should also be considered as a risk factor for drug-induced LQTS. An analysis of medication lists from 1.1 million patients showed 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.²³

Conclusions

Drug-induced LQTS should always be considered as a predictor of sudden cardiac death, and should thus prompt a 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 the 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 an LQTS-associated channelopathy. The field of pharmacogenetics may provide further insight into how mutations and polymorphisms in genes encoding cardiac ion channels modulate the response to certain therapeutic agents.

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