Cardiovascular Drugs Inducing QT Prolongation: Facts and Evidence

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Abstract: Acquired QT syndrome is mainly caused by the administration of drugs that prolong ventricular repolarization. On the other hand, the risk of drug-induced *torsades de pointes* is increased by numerous predisposing factors, such as genetic predisposition, female sex, hypokalemia and cardiac dysfunction. This adverse reaction is induced by different chemical compounds used for the treatment of a variety of pathologies, including arrhythmias. As it is known, antiarrhythmic agents and other cardiovascular drugs can prolong the QT interval, causing this adverse reaction. Of the 20 most commonly reported drugs, 10 were cardiovascular agents and these appeared in 348 of the reports (46%). Class Ia antiarrhythmic agents have frequently been linked to inducing arrhythmia, including *torsades de pointes.* Sotalol and amiodarone, class III antiarrhythmics, are known to prolong the QT interval by blocking I_{Kr}. Due to the severity of events caused by the therapeutic use of these drugs, in this work of revision the cardiovascular drugs that present this property and the factors and evidence will be mentioned.

Keywords: QT interval, drug-induced *torsades de pointes*, antiarrhythmic drugs, amiodarone, sotalol, HERG channel.

INTRODUCTION

The prolongation of the QT interval of the electrocardiogram has either a congenital origin due to mutations in ion channels or an acquired origin, generally due to the administration of QT-prolonging drugs [1]. The prolongation of this segment is related to the appearance of early post-potentials and the increase of the dispersion of the QT period in the different layers of the myocardium [1]. These electrophysiological abnormalities give rise to TdP, also called polymorphic ventricular tachycardia, which usually causes syncope, ventricular fibrillation and sudden death [2]. This adverse reaction is induced by different chemical compounds used for the treatment of a variety of pathologies, including arrhythmias. As it is known, antiarrhythmic agents and other cardiovascular drugs can prolong the QT interval, causing this adverse reaction. Due to the severity of events caused by the therapeutic use of these drugs, in this work of revision the cardiovascular drugs that present this property and the factors and evidence will be mentioned.

DRUGS THAT MAY CAUSE QT PROLONGATION OR *TORSADES DE POINTES*

In his review, Darpö [3] wrote that, in all, 225 pharmaceutical compounds have been associated with *torsades de pointes* (TdP) in spontaneous adverse reaction reports collected by the WHO Drug Monitoring Centre. Of the 20 most commonly reported drugs, 10 were cardiovascular agents and these appeared in 348 of the reports (46%).

On the other hand, several drugs have been withdrawn from the U.S. market or have received black box warnings due to their potential to cause QT interval prolongation that leads to fatal ventricular arrhythmias and sudden cardiac death [4, 5]. Table **1** lists some cardiovascular drugs capable of prolonging the QT interval.

Table 1. Antiarrhythmic and Cardiovascular Drugs that Induce QT Prolongation

Generic Name	Risk
Antiarrhythmics	
Amiodarone	A
Disopyramide	A
Dofetilide	A
Flecainide	B
Ibutilide	A
Procainamide	A
Quinidine	A
Sotalol	A
Cardiovasculars	
Bepridil	A
Dobutamine	B
Dopamine	B
Adrenaline	B
Indapamide	B
Isradipine	B
Moexipril	B
Nicardipine	B

A: Drugs with a risk of *Torsades de Pointes*.
B: Drugs with a possible risk of *Torsades de Pointes*.
C: Drugs with a conditional risk of *Torsades de Pointes*.
Source: www.torsades.org (June 17 2009)

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The ability of a drug to prolong the QT period is related to the interference of inward and outward ionic currents in ventricular action potential [6]. Most of the drugs that exhibit this property increase the duration of the action potential by reducing the delayed rectifier potassium current, due to a blockade of the current's rapid component (I_{Kr}) [7].

In the ventricles, loss of function mutations in the genes which encode K^+ channels and drugs (mainly HERG channel antagonists) are related to hereditary and acquired long QT syndrome, respectively, that put individuals at high risk for developing TdP arrhythmias and life-threatening ventricular fibrillation [8]. Similarly, K^+ channel down-regulation in heart failure also increases the risk of sudden death [8].

On the other hand, the prolongation of the QT period of the electrocardiogram is used as a marker of a drug's ability to induce TdP [4]. Nevertheless, the relation between the prolongation of the QT interval and the incidence of this arrhythmia is imperfect. Drugs like amiodarone and verapamil, which prolong the interval significantly, show a low incidence of polymorphic ventricular tachycardia [9]. This is explained because these drugs present other actions, such as the blockade of L-type calcium channels which diminish the capacity to cause early post-potentials [10]. This suggests that it is important to consider not only a drug's ability to prolong the QT interval, but also possible pharmacological properties that diminish the alterations of the increase of action potential duration. It is currently generally accepted that the dispersion of the QT interval caused by a drug may be a more reliable parameter of the potentiality of a drug to cause TdP, since a greater dispersion of the QT interval facilitates the maintenance of this arrhythmia by a re-entry mechanism [11]. The incidence of TdP due to clinical drug use prolonging the QT interval is not well known [12]. The data of incidence of this adverse reaction are obtained mainly from spontaneous reports of adverse events. According to an epidemiological study carried out in Sweden, the incidence of TdP is estimated to be 10 times greater than the incidence reported [13]. In the case of antiarrhythmic drugs, like quinidine, the incidence of this adverse reaction is higher than 1% [5]. The incidence of this proarrhythmia due to class III antiarrhythmic drugs varies from drug to drug. Sotalol and dofetilide present a 3% risk, whereas amiodarone and azimilide present an extremely lower incidence [14]. This smaller incidence may be related to the ability of amiodarone and azimilide to block the rectifier current, Ikr as well as Iks [14].

Because the information on drug-associated TdP is constantly growing in line with the increasing awareness and concern, we kindly ask the reader to use the Internet for updates. The www.torsades.org website provides updated information about QT-prolonging agents.

FACTORS FOR DRUG-INDUCED QT PROLONGATION AND *TORSADES DE POINTES*

Table **2** [5, 15] shows some risk factors for induction of long QT intervals and TdP. Factors include genetic predisposition, gender, drug use, drug interactions and cardiac abnormalities.

Genetic Predisposition

It is widely known that congenital long QT syndrome is related to the existence of mutations in ion channels that take part in the processes of depolarization and repolarization of myocardial cells, which is also a factor in drug-induced TdP [8, 16]. On the other hand, although these mutations are rare (1 in 500 patients) [16], the existence of patients with ion channel mutations that present subclinical long QT syndrome has been established in recent years [17, 18]. Although these patients present a normal or slightly increased QT interval, they are more likely to exhibit QT interval prolongation from exposure to drugs, since they would present a reduced repolarization reserve [19]. Therefore, whereas the administration of QT-prolonging drugs would have minimum effects in normal patients, in patients with silent ion channel mutations, the administration of these drugs would cause an exaggerated prolongation of this interval and a greater risk of proarrhythmia [19]. A possible explanation may be the presence of a subclinical mutation of the intervening ion channel in the slow component of the delayed rectifier current (I_{Ks}). This mutation would not be significant in normal conditions due to the predominant role of I_{Kr} in repolarization, but it would be substantial if it was blocked. The presence of silent mutations was identified in 15% of patients with acquired long QT syndrome [20, 21]. On the other hand, genetic alterations also affect the plasma elimination of drugs, giving rise to greater plasma drug levels and a greater risk of TdP. It is known that the increase of plasma levels of most QT-prolonging drugs is dose-dependent, thus causing a greater prolongation of ventricular repolarization [22]. Two metabolic enzymes that present genetic polymorphism are CYP2D6 and CYP2C cytochrome P450 isoforms [22, 23]. Thus, there are people with fast metabolism with an enzyme with normal metabolic capacity, and people with slow metabolism with an aberrant enzyme. In Caucasians, the population with slow metabolism represents between 5% and 10% of total population. Several QT-prolonging drugs are metabolized by the CYP2D6 and CYP2C enzymes. These patients, when presenting deficient purifying capacity, will present high plasma levels and a greater risk of dose-dependent adverse reactions. Another protein involved in pharmacokinetic processes is P-glycoprotein, which takes part in the body's drug extrusion in the gastrointestinal tract and the kidneys [24]. A fraction of the P-glycoprotein population expresses one anomalous transporter, presenting a smaller capacity of extrusion and therefore increased plasma levels of those drugs that are substrates for this glycoprotein, such as amiodarone, digoxin and quinidine [25].

Table 2. Some Risk Factors for Drug-Induced *Torsades de Pointes* [5,15]

- Congenital long QT
- Female gender
- Hypokalemia, hypomagnesemia and hypocalcemia)
- Diuretics
- Bradycardia
- Cardiac hypertrophy and myocardial fibrosis
- Congestive heart failure
- Renal and liver insufficiency
- Co-administration of agents blocking P450 isoenzyme CYP3A4
- Baseline electrocardiographic abnormalities

Physiological and Pathological Factors

The QT interval of the electrocardiogram and its drug-induced prolongation can be increased by physiological and pathological factors. It is widely known that women present a longer QT interval than men, besides exhibiting a greater susceptibility to drug-induced prolongation [14]. Two thirds of the cases of TdP induced by reported drugs were observed in women [14]. On the other hand, anorexia nervosa, which affects 1% of young women, causing sudden death in a significant percentage of patients, appears to be related to an additional prolongation of the QT interval, which could be explained by electrolyte disorders as well as by unknown factors [26]. Bradycardia also favors the prolongation of the QT interval, which suggests that the effect drug-induced prolongation will be marked in patients with bradycardia or atrioventricular conduction problems [27]. Since the length of the interval is dependent on the heart rate, the interval should be corrected [28]. Other widely-known factors are electrolyte disorders. Hypokalemia and hypomagnesemia favor a greater prolongation by drugs [5, 15, 29, 30]. Renal and hepatic perfusion is reduced in patients with cardiac dysfunction, favoring smaller systemic drug elimination [14].

Myocardial alterations induced by acute myocardial infarction and left ventricular hypertrophy also favor a greater prolongation of the QT interval, as well as a greater dispersion between the different layers of myocardial cells [31]. On the other hand, heart failure causes an exaggerated prolongation of repolarization in canine Purkinje fibers [32].

Various forms of cardiac disease and rhythm disturbances result in altered ion channel and transporter function. These alterations appear in many instances to be part of the homeostatic adaptive response to the primary dysfunction, but then results in secondary cardiac dysfunction, including tachyarrhythmias. So, heart disease modifies the operation of ion channels and transporters in a way that induces the occurrence of rhythm disturbances through the arrhythmogenic remodeling process [33].

K^+ currents play an important role in shaping the cardiac action potential, and remodeling-induced changes in K^+ currents are important contributors to repolarization abnormalities associated with heart failure. Some of the changes in heart failure mimic congenital channelopathies that produce long QT syndromes, and congestive heart failure can be viewed like an acquired QT prolongation [33, 34]. Down-regulation of transcript expression plays a role in the changes in K^+ current function associated with heart failure. Posttranscriptional and posttranslational mechanisms may be important in heart failure-related I_{Ks} down-regulation, a fact that would not be surprising in view of the regulation of I_{Ks} function by associated proteins in macromolecular complexes [33,35]. The down-regulation of K^+ currents can promote arrhythmogenic early afterdepolarizations, either by prolonging action potential duration in the voltage range at which I_{CaL} reactivation generates afterdepolarizations or by reducing the repolarization reserve [36-38].

On the other hand, cardiac failure has effects on cellular Ca^{2+} handling. Triggered activity related to delayed afterdepolarizations caused by spontaneous diastolic Ca^{2+} release is a mechanism underlying ventricular arrhythmias induced by cardiac failure [33, 39, 40]. Delayed afterdepolarizations occur in congestive cardiac failure despite reduced Ca^{2+} stores because of some features of heart failure-induced ion transport remodeling [33, 40-42]: I) hyperphosphorylated Ca^{2+} release channels are prone to spontaneous diastolic Ca^{2+} release, II) for any given level of Ca^{2+} release, enhanced Na^+-Ca^{2+} exchange function increases the depolarizing current resulting from electrogenic Ca^{2+} extrusion, and III) I_{K1} down-regulation increases membrane resistance, resulting in a larger depolarization for a given inward current.

In the ventricle, electrical remodeling has been related to changes in T-wave morphology [43]. Moreover, ventricular remodeling is associated with prolongation of repolarization [44-46]. Rapid ventricular pacing for shorts periods (1 h) can cause changes in ventricular repolarization and changes in activation sequence over 3 weeks was associated with reduced expression of I_{to} and I_{to} channel mRNA [44-46]. On the other hand, the electronic load imposed by a change in activation sequence reduces the upstroke amplitude, which, in turn, attenuates I_{to} triggering down-regulation of the ionic current [47].

DRUG INTERACTIONS

The simultaneous use of drugs that induce prolongation of the QT interval is another risk factor for TdP. This risk factor can be avoided by the correct prescription of drugs. Drug-induced prolongation of the QT interval can be increased by the joint administration of another drug with the same pharmacodynamic property, or drugs that inhibit the systemic elimination of drugs that reduce plasma potassium levels [12]. On the other hand, agents with sympathomimetic activity also promote drug-induced TdP, since they increase calcium influx through L-type channels [10]. Numerous reports have shown a risk of proarrhythmia increased by association of two drugs that prolong ventricular repolarization [12]. Considering the high rate of prescription of these drugs, and that they are used for the treatment of different pathologies, it would not be strange for a patient to be prescribed two drugs with the same property. Viskin *et al*. [12] reviewed the reports of 229 cases of drug-induced TdP, finding that in 39% there had been joint administration of two QT-prolonging drugs. It is also worth noting that this drug interaction is easily avoidable by knowing the pharmacodynamic properties of interacting drugs. Listings of QT-prolonging drugs are available on websites such as www.torsades.org, which is regularly updated. Consulting these bibliographical sources could help avoid this type of potentially fatal drug interaction. In addition, if a patient who is under treatment with a QT-prolonging drug requires the administration of a drug of another pharmacological class, the physician should select the drug within the class with the smaller potential for prolonging ventricular repolarization. A great amount of QT-prolonging drugs is eliminated through hepatic metabolism by various cytochrome P450 isoforms. So, it has been demonstrated that the administration of erythromycin (a CYP3A4 inhibitor) significantly increases the levels of quinidine (a substrate of the CYP3A4 enzyme), increasing the risk of TdP [48, 49].

We also need to consider that several drugs, including thiazide diuretics and β agonists, cause hypokalemia and therefore exacerbate the drug-induced prolongation of the QT interval [50]. For example, the diuretic indapamide induces hypokalemia and blocks the slow component of the delayed rectifier K^+ current (I_{Ks}) and potentiates the effects of sotalol, leading to excessive lengthening of cardiac repolarization and to the development of TdP [51, 52].

ANTIARRHYTHMIC AND CARDIOVASCULAR DRUGS THAT MORE COMMONLY CAUSE *TORSADES*

Antiarrhythmic Drugs

Class Ia antiarrhythmic agents have frequently been linked to inducing arrhythmia, including TdP, by blockade of K^+ current, similarly to class III agents [3, 53, 54]. Sotalol and amiodarone, class III antiarrhythmics, are known to prolong the QT interval by blocking the I_{Kr}. However, the risk of TdP with amiodarone is low when compared with sotalol [3, 53, 54]. Higher drug concentrations of sotalol can lead to QTc intervals that are prolonged by approximately 10 to 40 milliseconds, thereby increasing the incidence of TdP. With the exception of quinidine, the degree of QT prolongation linked to the antiarrhythmics depends on the serum drug level [55].

On the other hand, the class III agents blocking the IKr and the human channel is encoded by the human ether-a-go-go-related gene (HERG) [8, 56]. The inhibition of HERG K^+ currents causes lengthening of the cardiac action potential and may produce beneficial class III antiarrhythmic effect. In contrast, an excessive reduction of these currents due to either genetic defects or adverse drug reactions can lead to hereditary or acquired long QT syndrome and an increased risk for TdP and sudden death [8, 56].

Class I Antiarrhythmic drugs

Disopyramide is a well-known antiarrhythmic agent with several indications for the treatment of arrhythmias [57]. Some precautions are electrocardiogram, monitoring and dose adjustment to prevent QT prolongation, and the correction of hypokalemia before initiating therapy [57, 58].

Disopyramide inhibits HERG-encoded potassium channels at clinically relevant concentrations and this action may constitute the molecular basis for acquired LQTS associated with this drug [59].

The class I antiarrhythmic agent procainamide is used for the treatment of ventricular tachycardia, premature ventricular contractions, paroxysmal atrial tachycardia, etc., and it is known to induce prolongation of the QT interval [10, 57]. Ellebongen *et al.* [60] recommend that patients being started on antiarrhythmic therapy with procainamide be admitted to the hospital for monitoring to ensure that their QT interval is not excessively prolonged.

Foo and Nq [61] reported the case of a 43-year-old Chinese woman who complained of a one week history of irregular rapid palpitations associated with chest discomfort and dyspnea, and a wide complex tachycardia with a slightly irregular rhythm. Delta waves were also present. When she was treated with intravenous procainamide, she developed TdP secondary to prolonged QT interval.

In their review about quinidine, Grace and Camm [62] wrote that syncope and sudden death have been recognized as potential complications of quinidine therapy and both are usually due to polymorphic ventricular tachycardia. The use of quinidine, one of the earliest antiarrhythmic drugs developed, fell dramatically in favor of newer antiarrhythmic medications when increased risk of ventricular arrhythmia and death with quinidine emerged [62, 63]. However, at this time there is a renewed interest in the use of quinidine. In particular, quinidine appears to be safe and efficacious in combination with verapamil for the treatment of atrial fibrillation. Quinidine has also been used successfully to treat idiopathic ventricular fibrillation, Brugada syndrome, and short QT syndrome [63].

TdP by quinidine also occurs during long-term treatment, usually in association with an identifiable trigger. It may occur in patients with a structurally normal heart but is more likely to occur in those with heart-muscle disease, in patients given quinidine combined with digoxin, or those with hypokalemia or hypomagnesemia [62]. It has been demonstrated that an inhibitor of the CYP3A4 significantly increases the levels of quinidine, increasing the risk of TdP [48, 49].

Quinidine-associated TdP is more common in women than in men, as is TdP associated with other antiarrhythmic drugs, possibly because of estrogen-dependent delayed repolarization [62]. It was estimated that quinidine can cause TdP in 1% to 8% of patients, even at lower doses [3]. The degree of QT prolongation linked to quinidine does not depend on the serum drug level [55, 62].

Flecainide is a class Ic antiarrhythmic agent that can block the delayed rectifier potassium current [64]. This agent is used as a provocative test to unmask the electrocardiogram (ECG) phenotype of the Brugada syndrome, as well as long-term treatment for long QT-3 syndrome, since it also shortens the QT interval [65]. Mutations of the cardiac sodium channel gene, SCN5A, are present in both long QT and Brugada syndromes [66]. Recently, Bernart *et al.* [67] reported a case where oral flecainide induced syncope with a Brugada ECG pattern in a patient with known long QT-3 syndrome.

Class III Antiarrhythmic Drugs

In their report, Letsas *et al.* [68] investigated the causative medications and underlying risk factors that predisposed to drug-induced QT interval prolongation in twenty-one patients with drug-induced long QT (90% females, mean age 64.3 ± 14.1 years). They reported that known cardiac agents (mainly class III antiarrhythmics) were implicated in 13/21 (62%), antipsychotics in 8/21 (38%), and antibiotics in 5/21 patients (24%). These authors observed a significant correlation between administration of cardiac agents and TdP events ($P < 0.05$).

Most of these class III agents, e.g. dofetilide, d-sotalol and sematilide, are powerful I_{Kr} blockers, but other mechanisms may also contribute to the antiarrhythmic effects (as may be the case with, for example, ibutilide and azimilide) [56]. Moreover, I_{Kr} is encoded by the HERG related gene and class III antiarrhythmic agents inhibit the HERG currents [56]. With amiodarone, the incidence of TdP is very low [69]. In several clinical trials, no proarrhythmia

occurred during treatment with intravenous amiodarone for conversion of atrial arrhythmias to sinus rhythm [70-72]. With d,1-sotalol, the incidence of TdP is about 2% [73-76]. With dofetilide, ibutilide and almokalant, the incidence varies between 1% and 8% [3].

Dofetilide is a highly specific class III methanesulfonanilide antiarrhythmic drug. This drug selectively blocks the rapid component of the cardiac ion channel delayed rectifier current and it works by selectively blocking the rapid component of the delayed rectifier outward potassium current, I_{Kr} [56]. The drug appears to primarily block activated channels and has a much lower affinity for closed and inactivated channels [77]. At nanomolar concentrations, this agent prolongs both the atrial and ventricular effective refractory periods and AP duration. Dofetilide does not appear to interact with other cardiac ion channels, and this explains its minimal effects upon conduction velocity, myocardial contractility and systemic hemodynamics. Dofetilide prolongs the QT interval with little effect on QT dispersion. No effect was observed on conduction parameters PA, AH, M HV, PR or QRS intervals, sinus cycle length or sinus node recovery [56].

In the Symptomatic Atrial Fibrillation Investigation Research on Dofetilide (SAFIRE-D) trial, the drug was evaluated for its ability to convert and maintain SR in patients with chronic atrial fibrillation (AF) (85% of patients) or atrial flutter. After the first 105 patients were enrolled, the dosing protocol was altered to adjust for baseline renal function (creatinine clearance) and change in QTc interval duration. There were two cases of nonfatal TdP considered a result of dofetilide therapy; both occurred within the first 3 days of therapy [56]. Prolongation of QTc duration accounted for 10 withdrawals, and one SD occurred. Dosage adjustment based on creatinine clearance or QTc prolongation was required in 33% of patients. As a result of this trial, starting therapy in the hospital and adjusting dosage based on creatinine clearance and QTc prolongation are required to minimize the risk of proarrhythmia [56].

Like other class III drugs, the prolonged QT interval occurring in the patients treated with dofetilide can be complicated by TdP. The incidence of TdP is dose-dependent, and is 0.3–10.5%. The risk appears to be dose-dependent, with an increased incidence of TdP associated with higher doses of dofetilide administered. The risk of inducing TdP can be decreased by taking precautions when initiating therapy, such as hospitalizing individuals for a minimum of three days for serial creatinine measurement, continuous telemetry monitoring and availability of cardiac resuscitation. Severity of heart failure (HF), female gender, and QTc duration make it possible to identify patients with a high risk of early TdP when treated with dofetilide. Patients with recent myocardial infarction (MI) had TdP less often compared with patients with chronic HF [78].

Ibutilide is a selective class III antiarrhythmic agent that when administered intravenously can terminate AF and atrial flutter. It is an antiarrhythmic medication that helps return the heart to its normal sinus rhythm [56, 57]. Ibutilide reduces abnormal electrical signals that cause AF by stabilizing the heart muscle tissue. Ibutilide is given intravenously. It acts for only a short period. The drug is used for the cardioversion of atrial flutter and AF, but it can cause TdP [56, 57].

Ibutilide may cause many side effects. It should be used carefully, and patients should be closely monitored for a minimum of 4 h in the hospital after receiving ibutilide. Cardiac side effects of ibutilide include rapid, uncontrolled heart rhythm: ventricular tachycardia (VT), nonsustained monomorphic VT, TdP or ventricular fibrillation (VF) [56, 57].

Higher drug concentrations of sotalol can lead to QTc intervals that are prolonged by approximately 10 to 40 milliseconds, thereby increasing the incidence of TdP [55]. The incidence of sotalol-induced TdP is 0.3% for a daily dose of 80 mg, ~1% for patients taking between 160 and 240 mg/day, and up to 5–7% for a daily dose of 480–640 mg [54]. The risk is much higher in women and those with renal or congestive heart failure, sustained ventricular tachycardia, and with concomitant use of diuretics and hypokalemia [54].

Recently, the review study by Aström-Lilja *et al*. [79] of the Swedish pharmacovigilance database reported that, among a total of 61,788 adverse reactions recorded between 1991 and 2006, 88 cases of TdP were identified. In these cases, 27 different suspected drugs were implicated. Cardiac drugs were involved in most reports (74%; 65/88), with sotalol being the most frequently suspected drug (57%, 58/88).

In a case report of cardiac side effects of sotalol, Srivastava *et al*. [80] reported that a 44 year-old woman anesthetized for a transplant nephrectomy, had several runs of ventricular tachycardia followed by ventricular fibrillation requiring 30 s of cardiopulmonary resuscitation, after which she reverted to sinus rhythm. Subsequent investigation found that she had toxic serum levels of sotalol, with a prolonged corrected QT interval on the electrocardiogram. She was started on sotalol while her renal graft was functioning well but it was not reviewed when the graft started to fail and she had to commence hemodialysis. This led to the accumulation of sotalol and explains her serum sotalol value of 7.1 mg/l on the day of the event and concentrations greater than 2.5 mg/l are generally considered toxic.

Yalta *et al*. [81] reported a case with a severely prolonged QT interval and TdP after an initial intake of low dose sotalol (80 mg), indicating a probable inherent individual oversensitivity to sotalol. Letsas *et al*. [82], regarding this last report, suggested that pharmacologic challenge with sotalol may successfully identify patients with normal QTc intervals and reduced repolarization reserve that are at increased risk to develop drug-induced long QT syndrome and TdP.

A curious case of suicide attempt was reported by Cherpanatath *et al*. [83]. These authors reported that a 62-year-old man was brought into the intensive care unit because of a cardiac arrest. After extensive resuscitation, including defibrillation, sinus bradycardia occurred with marked QT prolongation, followed by recurrent episodes of TdP. The hetero-anamnestic data revealed a suicide attempt with sotalol.

Although amiodarone is approved by the US Food and Drug Administration (FDA) only for refractory ventricular

arrhythmias, it is one of the most frequently prescribed antiarrhythmic medications in the United States. Amiodarone is among the most effective with the additional advantage of having little proarrhythmic potential [56]. The favorable efficacy profile of amiodarone during electrical remodeling, particularly the marked increase in amiodarone on atrial refractory periods prolongation in early electrical remodeling, may explain its superior clinical efficacy over existing antiarrhythmic drugs [84].

Amiodarone has a low incidence of cardiac adverse events. With amiodarone, the incidence of TdP is very low [3, 54]. In seven clinical trials, with a total of 882 patients, no proarrhythmia occurred during treatment with intravenous amiodarone for conversion of atrial arrhythmias to sinus rhythm [3].

In elderly women long-term amiodarone treatment could result of combined block of the rapid and slow delayed outward potassium current components, translated to the ECG in a (more than expected) prolonged QT interval, an augmented transmural dispersion of repolarization (TDR) and an interrupted T-wave [56]. The unequal regression of repolarization lengthening made it possible to individualize I_K current components in the inscription of the interrupted T-wave, which argues against the U-wave as a separate entity. Silent ion channel gene mutations or polymorphisms and down-regulation of beta-adrenergic activation of I_{Ks} may underlie the unusual repolarization behavior. The unequal regression over time of amiodarone induced repolarization lengthening could have clinical significance [56, 85].

CALCIUM ANTAGONISTS

Bepridil is a calcium antagonist which in some countries is labeled for use only in patients who are refractory to other antianginal drugs. Although it is no longer sold in the United States, it has been discussed as a possible option for the treatment of atrial fibrillation [86].

Bepridil is a multi-channel blocker acting to block calcium, potassium and sodium channels, and has characteristics similar to those of class III antiarrhythmic drugs. Reports have shown that bepridil also affects pharmacological cardioversion in a manner similar to that of class III antiarrhythmic drugs. Bepridil's success rate is, at most, 34–58%; hence, the conversion effect of bepridil alone is not always satisfactory [87-89].

Bepridil prolongs the QT interval and several cases of TdP have been described. In particular, sinus bradycardia and a prolonged QT interval are known proarrhythmic effects of bepridil, and the administration of bepridil at high doses is associated with the development of TdP [90, 91]. Yasuda *et al*. [91] have reported that TdP appeared in approximately 1% of patients with atrial flutter or fibrillation who received bepridil. They described *torsades de pointes* as manifesting with hypokalemia, particularly in elderly female patients.

DIURETICS

Diuretic-induced hypokalemia is believed to be the common underlying mechanism of TdP under certain circumstances. Indapamide-induced syncope has been described in a patient with long QT syndrome, and has been attributed to electrolyte disturbances (hypokalemia) [92].

Indapamide also displays direct effects on ionic currents. This diuretic blocks the slow component of the delayed rectifier K^+ current (I_{Ks}) and potentiates the effects of dl-sotalol on ventricular repolarization, leading to excessive lengthening of cardiac repolarization and predisposing to the development of TdP [51, 52]. Indapamide has been shown to inhibit the Na^+ (I_{Na}), ultrarapid delayed rectifier K^+ and transient outward K^+ currents in atrial myocytes [93].

Letsas *et al*. [94] described a drug interaction with indapamide. It was a case of acquired long QT and TdP ventricular tachycardia in a woman with systemic lupus erythematosus and hypertension receiving prednisolone and indapamide.

MISCELLANEOUS

Ambasilide is a class III antiarrhythmic which has been shown to block multiple cardiac channels including beta-adrenergic antagonism. Although the electrophysiological effects of ambasilide are characterized on the cellular level, its effects on an organ level have yet to be investigated. Ambasilide prolonged the RR, PQ, QRS, QT, and QTc in a concentration-dependent manner in either normal SR or with reduced heart rate (atriotomy). dP/dtmin was increased (became less negative) in the presence of increasing concentrations of ambasilide, whereas the vehicle produced less negative lusitropy.

Ambasilide demonstrated use dependence by prolonging QTc less at slower heart rates [56, 95].

Sematilide, a close structural analog of N-acetylprocainamide, is a class III agent which acts largely by delaying conduction. The electrophysiological profile of sematilide is consistent with the selective block of outward potassium currents and associated isolated lengthening of the ventricular effective refractory period and AP duration [56].

Sematilide exerts class III actions in patients: it prolongs QTc in a dose- and concentration-related fashion, does not alter PR or QRS, and slows heart rate at high concentrations. The relations between dose and total area under the time-concentration curve, dose and peak plasma concentration, and peak plasma concentration and increase in QTc were linear. QTc increases of approximately equal to 25% were seen at plasma concentrations of approximately equal to 2.0 mg/mL. The mean elimination half-life was 3.6 ± 0.8 h, and most of a dose (77 ± 13%) was recovered unchanged in the urine [56, 96].

Plasma concentrations greater than or equal to 0.8 mg/mL suppressed arrhythmias (5 patients) or aggravated them (3 patients), including 1 patient who needed cardioversion for an episode of TdP (2.7 mg/mL) [56, 97].

Mibefradil, a T channel blocker, was withdrawn after only one year on the market, largely due to numerous drug-to-drug interactions, since it inhibited both CYP3A4 and 2D6 isoenzymes [98]. Mibefradil also gave rise to QT prolongation and marked T-wave morphological changes that resembled those seen with selective class III antiarrhythmics, and this caused a considerable debate as to whether the drug had proarrhythmic potentials. There were

several reports of TdP in patients on mibefradil during its short time on the market, but it is not fully clear whether it was a proarrhythmic propensity of the drug or pharmacokinetic interactions with other drugs that prolonged the QT interval. In either case, it is noteworthy that the combination of mibefradil and class I and III antiarrhythmics was particularly harmful in a large trial on 2,590 patients with congestive heart failure [99].

Miyajima *et al*. [100] examined the effect of the angiotensin II receptor blocker valsartan on QT dispersion and the relationship between oxidative stress and QT dispersion in patients with essential hypertension. These authors concluded that antihypertensive therapy with valsartan reduces QTc dispersion and this may be related to the ability of valsartan to reduce oxidative stress in patients with essential hypertension.

Recently Abraham *et al*. [101] reported that exposure to catecholamines and beta-receptor agonists used routinely during procedures and diagnostic tests can precipitate all the features of stress cardiomyopathy, including cardiac isoenzyme elevation, QTc interval prolongation, and rapidly reversible cardiac dysfunction.

On the other hand, in a recent case report, Quan *et al*. [102] informed that, strikingly, QTc prolongation was induced along with syncope after dobutamine infusion in a patient with a mutation of the KNCQ1-gene encoding serine instead of glycine.

Aliskiren, not yet approved by the FDA for the treatment of hypertension, manages hypertension by direct renin inhibition [57]. The side effect profile for aliskiren has not yet been fully described. Recently Peitz *et al*. [103] described the first apparent report of aliskiren-induced QT prolongation resulting in TdP.

THERAPY: β-BLOCKER EFFICACY IN THE TREATMENT OF LONG QT SYNDROME

β-blocker efficacy in long QT syndrome type 1 is good but variably reported, and the causes of cardiac events despite beta-blocker therapy have not been ascertained. Recently Vincent *et al*. (2009) [104] carried out a retrospective study of the details surrounding cardiac events in 216 genotyped long QT syndrome type 1 patients treated with β-blocker and followed up for a median time of 10 years. Twelve patients (5.5%) suffered cardiac arrest (CA)/sudden death, but 11 of 12 (92%) were noncompliant (n=8), were on a QT-prolonging drug (n=2), or both (n=1) at the time of the event. The risk for CA/sudden death in compliant patients not taking QT-prolonging drugs was dramatically less compared with noncompliant patients on QT-prolonging drugs (odds ratio, 0.03; 95% confidence interval, 0.003 to 0.22; P=0.001). None of the 26 patients with CA before beta-blocker had CA/sudden death on beta-blockers. These authors state that β-blockers are extremely effective in long QT syndrome type 1 and should be administered at diagnosis and ideally before the preteen years. Moreover, β-blocker noncompliance and use of QT-prolonging drug could be responsible for almost all life-threatening "beta-blocker failures" [104].

On the other hand, the aim of a study by Erdil *et al*. [105] was to evaluate whether esmolol has an effect on QT interval during induction of anesthesia using etomidate and fentanyl in patients with known coronary artery disease. Sixty patients were prospectively randomized to either a control group or the esmolol group. In the esmolol group, QTc interval was significantly shorter compared to the control group ($p < 0.05$). The authors conclude that infusion of esmolol attenuated the QTc interval prolongation associated with tracheal intubation.

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