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Drug-Induced Q–T Prolongation

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In 1964, the clinical syndrome of "quinidine syncope" was reported in eight patients undergoing quinidine therapy for atrial arrhythmias. These patients manifested repeated episodes of ventricular arrhythmias as well as syncope during therapeutic use of quinidine. Sudden death after quinidine initiation was hypothesized to be due to previously unrecognized ventricular dysrhythmias [1]. *Torsade de Pointes* (TdP) was first described by Dessertenne and colleagues [2,3] in two reports of patients who developed ventricular tachycardia with variation in the amplitude and shape of the QRS (ie, "twisting of the points"). Since then, a great deal has been discovered concerning the cause of TdP, although the exact mechanism by which it occurs is still subject to debate. Currently, a growing list of drugs are noted to be associated with Q–T prolongation [4–8]. Some have also been associated with dysrhythmia and an increased risk for sudden death, presumed to be due to a dysrhythmia such as TdP. Recent drug withdrawals have underscored the importance of this issue. As our understanding of Q–T prolongation and TdP evolves, important clinical implications arise for practitioners prescribing drugs that may prolong the Q–T interval.

Pathophysiology

Normal cardiac electrophysiology

Cardiac contraction depends on the organized activity of the electrical conduction system and ventricular myocytes (ie, Purkinje cells, subendocardial myocytes, midmyocardial M cells, and subepicardial myocytes). The

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cardiac action potential is the fundamental basis of cardiac electrical activity. The surface electrocardiogram (ECG) records a summation of the action potentials across the entire myocardium.

In a normal Purkinje cell, the rapid influx of sodium ions in phase 0 causes the interior of the cell to become more positive (Fig. 1). During phase 1, the transient outward potassium current (I_{to}) allows the charge on the inner membrane surface to decrease. This decrease brings the cell slightly closer to its resting potential. During phase 2, voltage-dependent calcium channels open, allowing calcium ions to enter. This calcium influx, which sustains the positive charge within the cell, is reflected as the plateau of phase 2. The slowly activated potassium channel (I_{Ks}) allows the gradual efflux of potassium during phase 2, which balances the inward flow of calcium, and the net result is little change in the membrane potential. Later in phase 2, a more rapid potassium current (I_{Kr}) leads to the rapid repolarization of phase 3. This is known as the "rapid delayed rectifier" current. Late in phase 3, the "inward rectifier current" occurs when I_{K1} opens, allowing further potassium efflux and returning the cell membrane to its resting potential. In phase 4, the charge within the cell has returned to its resting potential, and sodium begins to enter the cell. This process moves the cell membrane potential toward the threshold again, and the next action potential may occur. A fifth potassium current (I_{ped}) remains throughout repolarization, causing the "pedestal current." Late phase 4 and phase 0 represent *depolarization* of the cardiac cell, whereas phases 1, 2, and 3 represent *repolarization*. Phases 0 to 3 correspond to systole, and phase 4 corresponds to diastole. Similar processes occur in other cardiac cells; however, each type of cardiac tissue has different concentrations of each kind of ion channel, and they thus have slightly varied patterns of depolarization and repolarization [9–15]. Cardiac M cells appear to be uniquely susceptible to blockade of potassium currents [16,17].

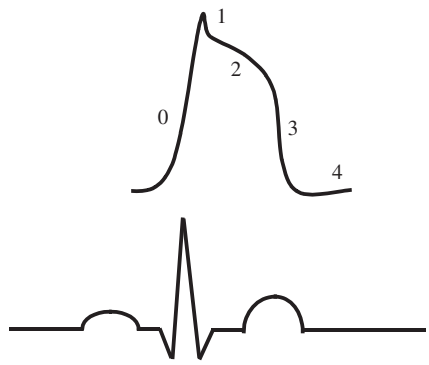

Fig. 1. Relationship between the action potential and the QRS. Changes in sodium influx during phase 0 lead to QRS prolongation, whereas blockade of potassium channels in phases 2 and 3 lengthens the Q–T interval.

Potassium efflux blockade and Q–T prolongation

As already discussed, repolarization in the cardiac conductive system is largely due to efflux of potassium from the myocardial cells. When potassium channels are blocked, repolarization is prolonged. Prolongation of repolarization is reflected in a prolonged Q–T interval and sometimes in the emergence of a U wave on the surface ECG (Fig. 2).

The Q–T interval on the surface ECG is measured from the beginning of the QRS complex to the point where the T wave reaches its isoelectric baseline. Ideally, this measurement should be made manually from an ECG limb lead and averaged over three to five beats [13,18,19]. The most important determinant of Q–T interval duration is the cycle length, or RR interval. Most heart rate "corrected" Q–T intervals, or QTc intervals, use Bazett's formula ($QTc = QT/RR^{1/2}$) or Fridericia's formula ($QTc = QT/RR^{1/3}$) [8,16]. Bazett's correction tends to overcorrect at high heart rates and undercorrect at low heart rates; Fridericia's correction may be more accurate at extremes of heart rate [19,20].

Q–T intervals vary substantially in the individual from beat to beat and are subject to respiratory, diurnal, and postprandial variation [7,8,21–24]. Although a Q–T interval of less than 440 milliseconds in men and less than 450 milliseconds in women is considered normal, prolongation of the Q–T interval to more than 500 milliseconds is considered to increase the risk for development of TdP [13,18,19,25–28].

Q–T prolongation may be familial or acquired. Patients with inherited long Q–T syndrome (LQTS), as in the Jervell-Lange-Nielsen and Romano-Ward syndromes, have congenital alteration in cardiac potassium or sodium channels. Hundreds of specific gene mutations (affecting genes KVLQT1, HERG, SSCN5A, CKNE1, MiRP1, and MinK, among others) have been identified to date, with the KVLQT1 (I_{Ks}) and HERG (I_{Kr}) mutations accounting for the majority of genotyped cases [29–32]. Clinically, patients

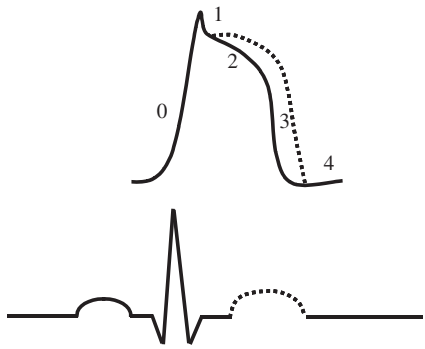

Fig. 2. Blockade of potassium channels and Q–T prolongation. Potassium efflux blockade slows repolarization in late phase 2 and phase 3, leading to prolongation of the Q–T interval.

with congenital LQTS have an increased risk for malignant dysrhythmia and sudden death, although the triggers and the recommended treatments vary with the mutation involved [17,33]. An estimated 5% to 10% of "silent" gene carriers manifest a normal Q–T interval at baseline, however, and are still considered at increased risk for syncope, TdP, and sudden death [13,17].

Acquired Q–T prolongation is most commonly drug induced but may be exacerbated by patient risk factors, such as bradycardia or hypokalemia [5,9,16,20]. Blockade of the delayed rectifier current I_{Kr}, which is encoded by the human ether-a-go-go (HERG) gene, has most often been associated with drug-induced Q–T prolongation, linking this syndrome mechanistically with congenital LQTS type 2, an inherited HERG mutation [11,16,17,26,34,35]. Unfortunately, the relationship between blockade of I_{Kr} and clinical proarrhythmia is not parallel. For example, amiodarone and verapamil, which both prolong Q–T intervals clinically and block I_{Kr} in cardiac myocytes, are not generally associated with TdP [12,20,35].

Q–T prolongation and Torsade de Pointes/sudden death

Q–T prolongation, whether familial or acquired, is considered a risk factor for the development of clinical dysrhythmia, particularly TdP, a form of polymorphic ventricular tachycardia. Nonsustained TdP may be asymptomatic or may manifest clinically as palpitations or syncope. However, sustained TdP may degenerate into ventricular fibrillation, leading to cardiac arrest.

The prolongation of the Q–T interval alone is not sufficient to cause TdP; other synergistic factors appear to contribute to the generation of dysrhythmia. One model proposes that, in the presence of a susceptible substrate (such as inherited ion channel defects or undiagnosed coronary disease), transient initiating events (ie, drugs, electrolyte imbalance) combine with electrophysiologic arrhythmia mechanisms to produce TdP and sudden death [33]. A consistent relationship between the length of the Q–T interval and the risk for TdP or sudden death is not clearly established; the relationship may vary from drug to drug and from individual to individual. Hundreds of drugs are known to prolong the Q–T interval, with widely variable degrees of evidence for clinical dysrhythmias [6,8,14,20,28,36].

The pathophysiology of TdP appears to rely on the initiation and then propagation of triggered activity. When membrane repolarization is disrupted during phase 3 of the action potential by potassium efflux blockade, increased positivity within the cell results in early afterdepolarizations (EADs) (Fig. 3). EADs may trigger aberrant beats that, in a vulnerable substrate, precipitate re-entry phenomena. Re-entrant arrhythmias occur when electrical impulses travel in a circular fashion within cardiac conduction tissue rather than moving outward and then stopping. When ion channels are functioning abnormally, as occurs in drug-induced Q–T prolongation,

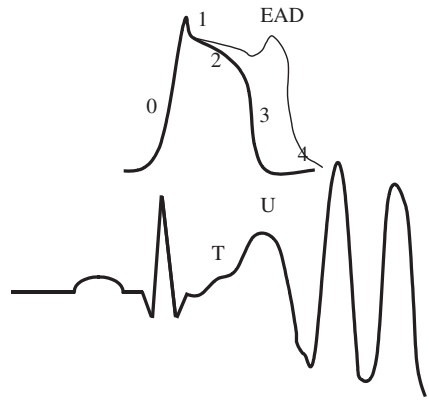

Fig. 3. The production of early afterdepolarizations and TdP. The retention of potassium ions within Purkinje cells leads to a ''refiring'' of the cell and the production of an early afterdepolarization. This may lead to the onset of TdP, which is heralded by a slowing of the rate and a prominent U wave.

a potentially unstable electrophysiologic milieu is produced. Repolarization occurs aberrantly throughout the conductive system. Heterogeneity of repolarization leading to asynchronous recovery of conductive cells may predispose to the re-entry phenomenon that propagates the dysrhythmia. The changing morphology of the QRS that is characteristic of TdP may be explained by variable predominance of two ectopic foci [11,12,16,31]. Electrocardiographically, a ''short-long-short'' ventricular interval precedes the onset of TdP, often associated with a prominent U wave (Fig. 4). The ventricular beats characteristically have an increasing, then decreasing amplitude as if twisting about the long axis [5,8,16,26,30,37].

''Q–T dispersion,'' defined as the difference between the shortest and the longest Q–T interval measured in the 12 lead ECG, has been used to reflect the heterogeneity of ventricular repolarization [17,38]. A normal Q–T dispersion is in the range of 40 to 60 milliseconds. Absolute values of 100 milliseconds or changes of more than 100% from baseline have been considered potentially significant, although this method of measurement of Q–T dispersion has not been shown definitively to assist in risk stratification

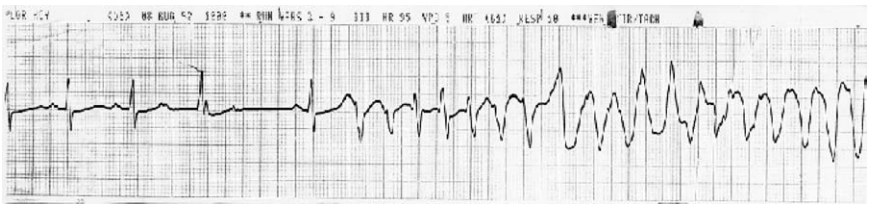

Fig. 4. TdP in a patient suffering from chronic procainamide toxicity. Note the characteristic ''short-long-short'' interval before the initiation of the arrhythmia.

[13,18,28,38,39]. In addition to Purkinje cell activity, dispersion of repolarization may also take place in M cells, which are located in the ventricular midmyocardium and have unique electrophysiologic properties [16]. M cells appear to be very sensitive to the effects of medications that prolong the action potential duration [17]. Preferential prolongation of the action potential duration in M cells may amplify the repolarization heterogeneity intrinsic to the ventricular myocardium and contribute to the propensity to develop TdP [12].

Epidemiology

Population studies

An estimated 1 in 10,000 individuals is a carrier of the LQTS gene, and LQTS may result in 3000 to 4000 cases of sudden death per year in the United States [31]. Overall, an estimated 184,000 to 460,000 persons in the United States (or 84–200 per 100,000) per year suffer sudden cardiac death, defined as unexpected natural death from a cardiac cause occurring less than 1 hour from the onset of symptoms [6,33,40–43]. Although most of these deaths are attributable to coronary heart disease or structural abnormalities, at least some are attributable to arrhythmia, and at least some of these may be ascribed to drug-induced TdP [44,45].

The study of drug-induced TdP and sudden death is difficult, because the diagnosis is only certain when rhythm analysis is obtained at the time of death by means of an implanted or external ECG recording. Most cases of sudden death occur at home, not in a monitored setting [33,46]. Further confounding the issue, some disease states for which Q–T-prolonging drugs are prescribed (ie, psychiatric disorders, cardiac disease) are already associated with an increased risk for sudden death compared with the general population, even in the absence of drug therapy [28,36,47–49]. Longer Q–T intervals at baseline, even within the normal range, have been associated with mortality in some epidemiologic studies, although these data are somewhat confounded by the association of underlying cardiac disease with longer Q–T intervals [50–52]. However, a significant association sometimes exists between an increased incidence of sudden death and prescribed medications. For example, epidemiologic data have been able to demonstrate an increased risk for sudden death among psychiatric patients prescribed particular medications, such as phenothiazines and thioridazine [53–57]. It is assumed that even a small drug-induced increase in Q–T interval may confer some overall increased risk for TdP when large populations are exposed.

Spontaneous reporting of adverse drug events has been estimated to underreport the true incidence of an adverse drug event by at least tenfold [6]. However, reporting may increase with increased awareness of the issue, as has happened in recent years [8,16,28,58].

Terfenadine example

First-generation antihistamines were effective but often produced drowsiness. Terfenadine, a second-generation antihistamine, was one of the first "nonsedating" antihistamines. It was introduced in 1985 and became widely used, with more than 15 million prescriptions dispensed in 1991 [59]. Overall, more than 100 million patients are estimated to have been exposed to the drug [60]. In 1990, the first report of terfenadine-associated TdP was reported in a patient taking both terfenadine and ketoconazole [61]. This report prompted a 1990 "Dear Health Care Provider" letter to all practitioners warning of the potential for drug interactions. By 1992, 25 cases of ventricular dysrhythmias had been reported in association with terfenadine use. In response, the manufacturer modified the labeling of the drug in 1992 to include a "black box" warning against the risk of Q–T prolongation and TdP [62]. A black box warning is a mandatory label change, typically applied when serious adverse events are discovered for a drug. However, continued reports of adverse events and deaths eventually led to the withdrawal of both agents from the United States market in 1997 [63]. Labeling changes and warnings are not always associated with changes in prescribing behavior [64].

Terfenadine was found to be equipotent to quinidine in blockade of I_{Kr} in vitro [59]. It also became apparent that terfenadine is dependent on hepatic metabolism by cytochrome p450 enzyme CYP3A4 and that deaths and adverse events were commonly associated with the coadministration of terfenadine with CYP3A4 inhibitors, such as erythromycin or ketoconazole [63,65]. This deadly drug interaction may be implicated in 125 deaths [66]. Premarketing surveillance did not signal a problem, probably because the adverse event had low incidence and the trials tended to preselect patients without comorbidities or concomitant medication use [8,56]. A therapeutic dose of terfenadine was found to produce an average QTc prolongation of 6 milliseconds in healthy individuals and 12 milliseconds in patients who had underlying cardiovascular disease [60]. However, in healthy volunteers, a combination of terfenadine and ketoconazole resulted in Q–T prolongation from a mean of 416 milliseconds to a mean of 490 milliseconds [67].

Q–T-prolonging medications

Many medications have been associated with lengthening of the Q–T interval at therapeutic doses or serum concentrations (Table 1). Ion channel studies have demonstrated that blockade of potassium efflux, primarily the HERG-encoded delayed rectifier current (I_{Kr}), is caused by many agents that lengthen the Q–T interval [9,11,16,26,34,35]. Antiarrhythmic agents (quinidine, procainamide) have the highest potential to cause Q–T prolongation, because repolarization effects are a mechanism of their therapeutic efficacy. In particular, sotalol, dofetilide, and ibutilide are reported to prolong the

Table 1
Q–T-prolonging drugs and drug interactions

Category	Drug	This drug is metabolized by the following p450 isoenzymes	This drug inhibits the following p450 isoenzymes[a]
Antiarrhythmics	Amiodarone (type III)	3A4	1A2, 2C9, 2D6, 3A4
	Dofetilide (type III)	3A4	
	Ibutilide (type III)		
	Sotalol (type III)	—	
	Disopyramide (type IA)	3A4	
	Procainamide (type IA)		
	Quinidine (type IA)	3A4, 2D6	3A4
	Encainide (type IC)	2D6	
	Flecainide (type IC)	2D6	
Calcium antagonists	Bepridil		
	Diltiazem	3A4, 1A2	3A4
	Verapamil	1A2, 3A4	3A4
Psychiatric	Amitriptyline	1A2, 2C9, 2C19, 2D6	
	Chlorpromazine	2D6	
	Desipramine	2D6	2D6
	Droperidol	3A4	
	Fluoxetine[b]	2C9, 2D6	2C19, 2D6
	Fluvoxamine[b]	1A2, 2D6	1A2, 2C19, 2C9, 3A4
	Haloperidol	1A2, 2D6	2D6
	Imipramine	1A2, 2D6, 3A4	
	Lithium	—	
	Pimozide	3A4	
	Paroxetine[b]	2D6	2D6
	Sertraline[b]		2C9, 2D6
	Thioridazine	2D6	2D6
	Ziprasidone	3A4	
Antihistamine	Astemizole	3A4	
	Diphenhydramine Hydroxyzine		2D5
	Terfenadine	3A4	
Anti-infective	Amantadine	—	
	Ciprofloxacin[b]		1A2, 3A4
	Chloroquine		
	Clarithromycin		3A4
	Erythromycin	3A4	3A4, 1A2
	Fluconazole[b]		3A4, 2C9

Table 1 (*continued*)

Category	Drug	This drug is metabolized by the following p450 isoenzymes	This drug inhibits the following p450 isoenzymes[a]
	Grepafloxacin	1A2	1A2
	Itraconazole[b]	3A4	3A4
	Ketoconazole[b]		3A4
	Pentamidine		
	Quinine		
Antiretroviral	Amprenavir[b]	3A4	3A4
	Indinavir[b]	3A4	3A4
	Ritonavir[b]	3A4	2D6, 3A4
Other	Arsenic		
	Cisapride	3A4	
	Grapefruit[b]		3A4
	Methadone	2D6, 3A4	2D6
	Organophosphates		
	Vasopressin		

[a] Concomitant administration of a p450 isoenzyme inhibitor with a drug that is metabolized by the same p450 isoenzyme may result in supratherapeutic drug levels and therefore an increased risk of Q–T prolongation/TdP. Some medications may inhibit their own metabolism.

[b] These medications are unlikely to significantly prolong Q–T interval at therapeutic doses but do inhibit the metabolism of other drugs associated with Q–T prolongation.

Data from Refs. [4,16,27,72,73,109].

Q–T interval by more than 50 milliseconds at therapeutic doses and have a high enough risk for TdP (over 1%) that inpatient cardiac monitoring is recommended with their initiation [68–71]. Other medications associated with Q–T prolongation or TdP include psychiatric medications (thioridazine, chlorpromazine, haloperidol, lithium), antihistamines (terfenadine, astemizole, diphenhydramine), anti-infective agents (erythromycin, clarithromycin, chloroquine, amantadine, grepafloxacin), and others, such as cisapride, arsenic, and methadone.

Medications that prolong the Q–T interval are not always associated with TdP, and medications associated with TdP do not always prolong the Q–T interval [6–8,13,14,20,28,36,56]. In addition, some medications associated with Q–T prolongation and TdP at therapeutic doses are less associated with TdP at toxic doses. The many pharmacologic actions of medications likely contribute to these phenomena. For example, amiodarone causes blockade of I_{Kr} and clinically results in significant Q–T prolongation, but TdP is rarely reported. This pattern is probably due to amiodarone's other pharmacologic actions, such as blockade of sodium and calcium currents [35] and suppression of M-cell action potential duration [12]. Quinidine causes blockade of I_{Kr} at therapeutic concentrations and is associated with prolonged Q–T and TdP. However, at toxic concentrations, increased blockade of sodium channels occurs, which results in decreased heterogeneity of repolarization and may explain the relatively lower incidence of TdP

at toxic levels of quinidine [12]. Finally, tricyclic antidepressants, such as amitriptyline, cause blockade of I_{Kr} and Q–T prolongation. However, TdP is uncommon in tricyclic antidepressant overdoses, perhaps partially because of the significant tachycardia resulting from the anticholinergic effects of these drugs.

Updated lists of medications associated with Q–T prolongation and TdP may be found at http://www.torsade.org [4]. Medication-based risk stratification has also been proposed [14].

Drug interactions

Drug interactions resulting in Q–T prolongation or TdP may be pharmacodynamic (additive effects of two Q–T-prolonging medications), pharmacokinetic (one drug interferes with the metabolism of another drug), or both (see Table 1). In many cases of drug-induced Q–T prolongation and TdP, supratherapeutic or toxic drug levels are implicated [5,8,28]. Where drug-induced Q–T prolongation is dose dependent, inhibition of metabolism may result in toxic drug levels and increase the risk of TdP. Hepatic cytochrome p450 (particularly CYP 3A4) inhibitors that block metabolism of the parent compound may lead to Q–T prolongation and have been associated with TdP. Medications reported to interfere with metabolism of drugs associated with TdP include antifungals (ketoconazole, fluconazole), antidepressants (fluoxetine, fluvoxamine, sertraline), HIV agents (indinavir, ritonavir, amprenavir, saquinavir), calcium channel blockers (diltiazem, verapamil), and antibiotics (erythromycin, clarithromycin, ciprofloxacin) [19,30,72,73]. Grapefruit, which contains the CYP 3A4 inhibitor naringenin, has also caused increased concentrations of drugs metabolized by CYP 3A4 [74,75]. In addition, medications associated with electrolyte disturbances, such as diuretics, may predispose a patient to develop drug-induced Q–T prolongation and TdP. After rapid intravenous infusion of a Q–T-prolonging agent, the risk of Q–T prolongation and TdP may also be exaggerated [76].

Risk stratification

Some patients may be at greater risk for developing TdP than others because of a genetic predisposition to arrhythmia (Box 1). Inherited defects of cardiac ion channels have variable penetrance, and not every carrier will manifest changes on a screening ECG. However, this patient population may be at increased risk when exposed to agents that block potassium channels and "unmask" their genetic predisposition to Q–T prolongation and arrhythmia [20,30,31,77]. This concept has been termed "repolarization reserve" [26]. In 98 patients who had drug-induced Q–T prolongation (>600 ms) or TdP, genetic testing showed that four had identifiable mutations, one of which was novel [78]. Genetic testing in another group of

Box 1. Risk factors for drug-induced Q–T prolongation

Pharmacologic factors

- Medication with intrinsic blockade of cardiac potassium efflux (particularly I_{kr})
- Concomitant administration of multiple medications known to prolong Q–T interval
- Supratherapeutic or toxic dosage of medication, resulting in high medication levels
- Concomitant administration of a Q–T-prolonging medication with an agent inhibiting its metabolism, resulting in high medication levels
- Concomitant administration of medications resulting in electrolyte disturbances (eg, potassium wasting diuretics) and medications known to prolong the Q–T interval
- Rapid intravenous infusion of agent known to prolong the Q–T interval

Individual factors

- Female gender
- Electrolyte disturbances (hypokalemia, hypomagnesemia)
- Bradycardia < 50 beats per minute
- Structural heart disease (cardiomyopathy, congestive heart failure, ischemia)
- Renal dysfunction
- Hepatic dysfunction
- Individual genetic ''repolarization reserve'' (mutations affecting cardiac ion currents)

Data from De Ponti F, Poluzzi E, Cavalli A, et al. Safety of non-antiarrhythmic drugs that prolong the QT interval or induce torsade de pointes: an overview. Drug Saf 2002;25(4):263–86; and Owens RC Jr. QT prolongation with antimicrobial agents: understanding the significance. Drugs 2004;64(10):1091–124.

92 patients with drug-associated TdP found five mutations, two of which were novel. Adding to this the known background of genetic polymorphism in LQTS genes MiRP1 and mink, these authors estimate that allelic variants contributing to the risk for drug-associated TdP may be identifiable in 10% to 15% of patients [79]. In a study of 1382 healthy adults, a common polymorphism in the HERG gene was found to be clinically associated with the length of the QTc interval, although these variations fell within the normal range [80]. In patients who have underlying genetic polymorphism and a normal screening ECG, the development of TdP with pharmacologic therapy may be truly idiosyncratic and unpredictable [72,81].

Female gender is associated with increased risk of TdP in both its congenital and acquired forms and with increased risk of arrhythmic sudden cardiac death. This association may be due to genetic differences in the number of potassium channels, to effects of estrogen, and to females' longer Q–T interval at baseline than males [30,45,82–85]. Patients who have heart disease are predisposed to disrupted ventricular repolarization and may have exaggerated effects with prescribed Q–T-prolonging medications [33,86]. Bradycardia (<50 beats per minute) is a risk for prolonged Q–T because of increased action potential duration that enhances the effects of I_{Kr} blockade [14]. The propensity for greater drug-induced action potential prolongation at reduced heart rate is termed "reverse use dependence" [9]. Electrolyte imbalances (eg, hypokalemia, hypomagnesemia) are themselves associated with prolonged Q–T interval; these effects are additive in the presence of Q–T-prolonging medications. Hypokalemia appears uniquely to predispose patients to Q–T prolongation [87]. Hepatic or renal dysfunction may result in disrupted drug metabolism, leading to supratherapeutic or toxic drug levels and an increased risk for adverse events, including Q–T prolongation [8,28]. Recent conversion from atrial fibrillation, particularly with a Q–T-prolonging medication, is also considered a risk factor for subsequent drug-induced Q–T prolongation [88].

It has been suggested that most patients with drug-induced TdP have easily identifiable risk factors. In 249 patients with TdP caused by noncardiac medications, a review of risk factors (female gender, cardiac disease, hypokalemia, drug toxicity from supratherapeutic dosing or impaired drug metabolism, drug interactions, prolonged QTc >450 ms on baseline ECG) was performed. More than 90% of the patients had one risk factor, and 71% had at least two of the risk factors [89]. It is likely that a combination of risk factors work in synergy in the individual patient to produce TdP [9].

Clinical implications

The prudent clinician is expected to weigh the risks and benefits before administering any drug. For drugs that may prolong the Q–T interval, a careful evaluation of risk factors for dysrhythmias should precede administration. Risk assessment for drug-induced Q–T prolongation should include careful consideration and integration of both patient and medication factors that may amplify the risk for TdP. In clinical practice, adverse effects due to Q–T-prolonging medications may be minimized by not exceeding recommended dosing of these medications, maintaining awareness of drug interactions, and avoiding their use in patients who have pre-existing risk factors, particularly when alternatives are available [13,16,19,20,26,53]. Screening ECGs may be obtained at the discretion of the practitioner before the initiation of medications known to prolong the

Q–T interval and at intervals thereafter, particularly if doses increase or new medications are added. A prolonged Q–T interval (ie, >500 ms) on a screening ECG may be an indication of congenital long Q–T syndrome or may reflect underlying electrolyte disturbances, cardiac disease, or current pharmacologic effect. When discovered, this should prompt careful consideration of further drug therapy and perhaps evaluation for other causes of Q–T prolongation [19,26]. After a Q–T-prolonging drug is prescribed, patients should be instructed to report any new symptoms, particularly palpitations, presyncope, or syncope [8,14,26,28].

In addition, caution should be exercised when prescribing newly approved medications, because rare events such as TdP may not manifest until medications are distributed to the population at large. Future genetic screening technology may allow for individualized risk assessment of adverse events with medications, such as an enhanced risk of Q–T prolongation or TdP [9,29,30,78].

Treatment of Torsade de Pointes

The management of patients who have drug-induced TdP is removal of the offending agent, replenishment of potassium if necessary, and intravenous infusion of magnesium [27,31,90]. Although magnesium will not decrease the Q–T interval, it will increase the activity of the magnesium-dependent sodium/potassium pump, leading to the reuptake of potassium ions in exchange for sodium ions. Magnesium also increases potassium efflux by the I_{k1} channel (inward rectifier current) [91]. Magnesium may be administered in a 1 to 2 g bolus and repeated if TdP does not resolve [92]. Serum potassium should be maintained in the high normal range [90,93]. Other treatments for TdP include the administration of isoproterenol and insertion of an overdrive pacemaker. Pacing at rates from 90 to 140 beats per minute may be required to suppress the dysrhythmia [90,92]. Both overdrive pacing and isoproterenol have had intermittent success and should be used only in cases of acquired LQTS; in patients with congenital LQTS, increased heart rate may promote arrhythmia [90]. Isoproterenol may be used in patients with significant bradycardia but should be avoided in patients with poor left ventricular function or severe coronary artery disease [94]. Defibrillation has been used with variable success. A potassium channel opener, nicorandil, has been shown to shorten the Q–T interval and suppress TdP in an in vitro model [95].

New drug approvals and monitoring

The US Food and Drug Administration (FDA) has a mission to ensure that safe and effective drugs are marketed. Before a pharmaceutical agent is approved for marketing, it must undergo a rigorous process involving preclinical and clinical studies to demonstrate safety and efficacy. This

process may take 3 to 10 years and cost as much as 100 million dollars. These studies may enroll up to 4000 patients and may only monitor patients for months to a few years [96–98]. Rare effects, such as TdP and sudden death, may not be observed until a large number of patients have been exposed to the pharmaceutical agent. Therefore, these early clinical studies do not provide absolute assurance of safety [96,99]. A recent review of 548 new chemical entities approved by the FDA from 1975 to 1999 revealed that 56 (10.2%) acquired a new black box warning or were withdrawn from the market during the study period. Of the 16 drugs withdrawn from the market, half were withdrawn within 2 years of approval, and five had received a new black box warning before withdrawal [100]. Q–T prolongation associated with dysrhythmia or TdP is the number one reason for withdrawals or restrictions of drugs over the past 10 years, including noncardiac medications such as cisapride, astemizole, terfenadine, and grepafloxacin [100]. These high-profile medication-related adverse events, in conjunction with our evolving understanding of Q–T prolongation and TdP and improved models for scientific study (ie, cloning of cardiac ion channels) have resulted in significant reassessment and modification of the process by which new drugs are studied before approval and marketing [8,13,26,99].

Preclinical studies of the effect of chemical entities on cardiac repolarization involve in vitro models. Medications may be studied for their effect on ion currents in cloned ion channels, HERG (I_{Kr}) blockade in disaggregated cells, action potential duration in isolated tissue (such as canine Purkinje fibers), and electrogram changes in isolated perfused hearts. Intact animal models are typically studied before phase I/II clinical studies [14,99].

Clinical studies are generally performed when the drug is considered sufficiently safe and meritorious to deserve further evaluation. Strict guidelines for the implementation of these studies have been difficult to formulate. Because the outcome of interest, sudden death due to TdP, is uncommon and difficult to assess, Q–T prolongation has become a surrogate marker for potential arrhythmogenicity and is commonly used in research and by regulatory agencies. The degree of Q–T prolongation is known to be an imperfect marker for arrhythmia. The ideal methods for measuring the Q–T interval are subject to debate [7,8,13,28,99,101,102]. Additionally, there is no consensus regarding the precise degree of Q–T prolongation that is clinically significant, although most would consider an absolute Q–T interval greater than 500 milliseconds or a medication-related change in the Q–T interval of more than 30 to 60 milliseconds to represent at least some risk [8,13,18,19,25–28]. From a regulatory perspective, the challenge is to determine whether Q–T interval changes are drug related, whether they confer risk, and, if so, which regulatory actions should be undertaken, such as restrictive labeling, further investigation, or abandonment of further study of the drug. Unfortunately, because a perfect model does not exist to

quantify torsadogenic risk, risk assessment is typically based on a conglomeration of all relevant data.

The FDA relies on postmarketing surveillance to ensure safety after a drug is marketed [97]. Data regarding adverse events are obtained from health care professional spontaneous adverse drug event reports (MedWatch program), manufacturer and hospital surveillance data, reports published in the medical literature, clinical and epidemiologic studies, and other relevant sources. Clinicians, however, are notoriously poor at reporting adverse drug events [103–105]. If the FDA receives sufficient reports of adverse events, it may launch a more thorough investigation, convene an advisory panel, and take action. The FDA may send advisories to health care professionals (''Dear Health Care Provider'' letters), recommend labeling changes, conduct further studies, or assist the manufacturer with drug withdrawal. When making these decisions, the regulatory agencies must balance risk assessment and patient safety issues with benefits expected from the drug in question. For example, two drugs with equal assessed risk for Q–T prolongation may be viewed differently if one drug is treating a life-threatening condition and the other drug is treating a less serious disorder or a disorder for which other, safer treatments exist [13,14,19,27,99].

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is an international group of regulatory authorities and experts from Europe, Japan, and the United States (available at: http://www.ich.org). The ICH Expert Working Group has drafted several guidelines regarding the nonclinical (S7B) and clinical (E14) evaluation of Q–T/QTc interval prolongation and the proarrhythmic potential of nonantiarrhythmic medications. These documents were presented in Washington, DC in June 2004 and are currently under discussion and review by experts [106–108]. The preliminary guidelines recommend that both new pharmacologic agents and established agents with new indications and dosing undergo thorough evaluation of the potential for Q–T prolongation, while recognizing that Q–T prolongation is an imperfect biomarker for adverse events. In preclinical testing, pharmaceuticals should undergo multiple assays to assess repolarization effects, including HERG current study, action potential duration study on canine Purkinje fibers, and study in an animal model. An integrated risk assessment is formulated based on the results of in vitro I_{Kr} studies, in vivo Q–T prolongation studies, pharmacologic class, and any other relevant information, such as known cases of adverse events.

If an agent is deemed suitable for clinical testing, a ''thorough Q–T/QTc study'' should take place in healthy volunteers to determine whether the agent has a threshold effect on cardiac repolarization. If the agent prolongs the Q–T/QTc by greater than 5 milliseconds or if adverse events of concern are reported, further investigation is needed. If the agent belongs to a class of drugs already known to prolong the Q–T/QTc interval, more rigorous measures may apply. Agents prolonging the mean Q–T/QTc interval by more

than 20 milliseconds are considered to have a substantial proarrhythmic potential. The results of these investigations may be grounds for nonapproval or discontinuation of drug development. These and other important regulatory initiatives will standardize the evaluation of the Q–T-interval–prolonging potential of new agents, and it is to be hoped that they will enhance overall patient safety.

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