Drug-Induced QT Prolongation

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The duration of QT interval on surface electrocardiography represents the time required for all ventricular depolarization and repolarization processes to occur. While QT prolongation by itself is not harmful, it provides the basis for the potential life-threatening ventricular tachyarrhythmia known as Torsades de pointes ("twisting of the points") due to its unique morphology of changing QRS amplitude [Figure 1A].

The development of TdP is the hallmark in patients with congenital prolonged QT syndromes, but several other conditions also expose patients to develop this arrhythmia. These include structural heart disease, situations causing significant bradycardia (e.g., complete atrioventricular block), metabolic derangement (hypokalemia, hypomagnesemia and hypocalcemia) [1], and a variety of medications (especially anti-arrhythmic drugs, non-sedating antihistamines, antibiotics and psychiatric drugs). QT prolongation became an important topic in drug development and post-marketing evaluation of adverse drug effects. The issue is therefore discussed in detail from a pharmacological point of view.

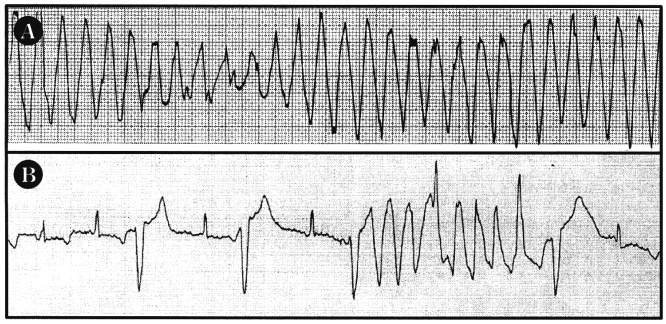

Figure 1. [**A**] Torsades de pointes. [**B**] Long-short sequence (ventricular extrasystole with post-extrasystolic pause) leading to Torsades de pointes.

Pathogenesis

Cardiac ventricular muscle action potential has several components [Figure 2]: phase 0 = rapid depolarization, phase 1 = early phase of repolarization, phase 2 = plateau, phase 3 = late phase of rapid repolarization, and phase 4 = resting membrane potential. Different ion currents (Na^+, Ca^{2+}, and K^+) flowing through specialized ion channels bring about the different phases. During the plateau phase there are inward currents of Na^+ and Ca^{2+} and an outward current of K^+, while during phase 3 repolarization there is mainly an outward current of K^+. Either an excess inward flow of Na^+ and Ca^{2+} or blockage of outward current of K^+ will cause a delay in repolarization, expressed on surface ECG as QT prolongation [2].

Under conditions of incomplete repolarization, spontaneous small depolarizations, known as "early after depolarizations," can occur. EADs are recognized on the ECG as tall U waves. When such depolarizations reach the membrane potential threshold, a premature beat occurs [3,4]. Propagation of this beat to create a sequence of TdP is due to successive focal activity, re-entrant excitation (created due to a non-homogeneous repolarization in different parts of the myocardium) or a combination of both mechanisms [4].

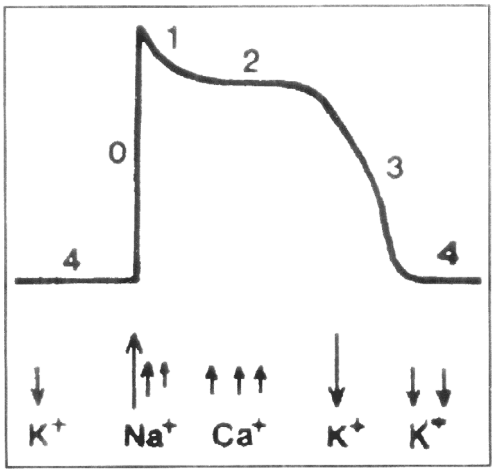

Figure 2. Cardiac muscle action potential with major ionic currents: Phase 0: rapid depolarization. Phase 1: early repolarization. Phase 2: plateau phase. Phase 3: rapid repolarization. Phase 4: resting membrane potential. ↑ Inward current ↓ Outward current.

QT interval duration depends on heart rate (see section: Assessment of QT interval), and since it is longer after a pause there is a higher propensity for EADs in this setting. This leads to a characteristic sequence known as the "long-short sequence" (in which TdP complexes are seen after pauses, most often post-extrasystolic pauses) before initia-

TdP = Torsades de points
EAD = early after depolarization

tion of the arrhythmia in patients with drug-induced TdP [3] [Figure 1B].

The drugs studied for their potential to prolong the QT interval and cause TdP do so by blocking the potassium channels participating in the repolarization phase [5]. Several factors predispose patients who are treated with drugs that prolong the QT to develop TdP. These include bradycardia, hypokalemia and hypomagnesemia, known to cause delay of repolarization [6]. There may be some genetic predisposition for the development of TdP during drug therapy [7], and females seem to be more prone than men to develop this tachyarrhythmia while on drug treatment [8].

Assessment of QT interval

While not fully agreed upon, some authors suggest that QT interval should be measured in lead II [9]. There may be several difficulties in QT measurement, especially during treatment with drugs affecting repolarization, due to changes in T wave morphology and appearance of prominent U waves [3]. The end of the T wave is determined by drawing a tangential line to the steepest part of the descending portion of the T wave, taking its intercept with the isoelectric line as the end of the T wave [10]. U waves should be included in the QT measurement if they are greater than 25–50% of the T wave [11]. Since QT length changes according to heart rate, several formulas were developed correcting the QT to rate (QTc). The most widely used formula is Bazett's formula ($QTc = QT / \sqrt{RR}$, in which the QTc represents the value of the QT interval normalized for a heart rate of 60 beats/min, in which RR interval is 1 sec) [10]. The normal QTc however can be quite variable during a 24 hour period and during different activities [12]. Moreover, in some situations (e.g., during complete AV block) documented TdP is more correlated with actual QT than with QTc [13]. In this regard, it may be more accurate to measure the QT interval under several heart rates in the same patient without applying any correction formula [10].

Baseline QT in women is approximately 20 msec longer than in men, with upper limits varying in several reports. QTc values more than 390–420 msec in men and more than 440 msec in women are prolonged [14,15]. It has been suggested that QT values above 600 msec portend an especially high absolute risk for development of TdP, but many patients develop this arrhythmia with much lower values [3].

During treatment, several ECG markers can be associated with a higher risk for TdP. These include: low amplitude broad and/or bifurcated T waves [3,16], T wave alternans, prominent U waves, extrasystoles, and U wave augmentation after an extrasystole [3]. Although controversial, another parameter that may be more indicative in assessing the risk for arrhythmia in patients with prolonged QT intervals is the QT dispersion (calculated as the difference between the maximum and minimum precordial QT intervals on a single ECG) [17]. The lead-dependent difference in QT duration represents the regional differences in ventricular repolarization times. It has been shown that the risk for TdP is associated with greater dispersion of either endocardial action potential duration or surface ECG QT interval [18].

Many drugs are reported in association with QT prolongation and TdP. We tried to include as many drug preparations as possible (source of information: MEDLINE and Internet search) with the knowledge that as this article is being published, new medications for QT prolongation are being added to the already long list.

Anti-arrhythmic drugs

Class IA drugs – namely quinidine, procainamide and disopyramide – are the most common drugs known to cause QT prolongation [6]. Quinidine, the drug most studied, is known to exert its effect on repolarization through blockade of potassium channels. The frequency of TdP in patients treated with quinidine is 0.5–9%, and occurs most often early in treatment (first 3–4 days) with relatively low (therapeutic or sub-therapeutic) drug levels. Many patients do not have a markedly prolonged QT interval. All class IA drugs are concordant in their ability to produce TdP (as with quinidine, with low drug levels during disopyramide treatment but in a dose-dependent manner with procainamide). Risk factors for the development of TdP in patients treated with Class IA drugs include congestive heart failure, baseline prolonged QT duration, bradycardia, hypokalemia and hypomagnesemia [1]. Amiodarone was found to be safe for treating arrhythmia in patients who developed TdP under treatment with Class IA drugs [6,18].

Class IB and IC do not affect ionic currents in a way that prolongs repolarization and thus do not produce QT prolongation or TdP. They may cause QRS prolongation and they do have pro-arrhythmic potential [6].

Class II drugs, the beta-blockers, do not have a direct effect on repolarization or QT interval and as a rule are not considered to cause TdP.

Drugs considered to have class III properties have different effects on QT prolongation. Sotalol and d-sotalol (which has only minimal beta-blocking activity) are known to cause QT prolongation and a 2–4% incidence of TdP [19]. In contrast to Class IA drugs, the effect of Class III drugs on QT prolongation is dose dependent. Females, patients with renal dysfunction or structural cardiac disease, and patients treated for ventricular arrhythmia are at higher risk [8,19]. Different studies have reported that the risk for TdP was 3–8.3% during treatment with ibutilide [20] and 3.3% during treatment with dofetilide [21], newer Class III drugs. The risk is higher among patients with advanced heart failure (FC III-IV). As with quinidine, most episodes of TdP due to sotalol, ibutilide and dofetilide occur within the first few days of treatment. There are no well-documented cases of TdP during treatment with bretylium, perhaps because it is

AV = atrioventricular

usually given in the acute management of ventricular tachyarrhythmia during which TdP may be missed [3]. Amiodarone, another Class III drug, can prolong the QT interval. TdP, on the other hand, is thought to be quite rare [6,18]. The reason for this is not fully understood, but there are some possible explanations. Amiodarone suppresses sodium as well as calcium currents [22]. Both ion currents when continued during phases 2–3 repolarization (Na^+ current by failure of inactivation) [2] can prolong repolarization and participate in production of EAD and TdP. Accordingly, amiodarone abolished EAD in animal models [22]. Amiodarone was also shown to decrease QT dispersion [18]. Amiodarone is considered by most authors to be relatively safe for patients with organic heart disease and those who previously developed TdP while on drug treatment [1,3,6,18].

Verapamil, the Class IV anti-arrhythmic drug, does not cause QT prolongation. However, several anti-anginal calcium channel blockers such as bepridil [23] and mibefradil were reported to cause QT prolongation and TdP. Another drug in this class is prenylamine, which was withdrawn from the market because of these side effects [24]. The dihydropyridines isradipine and nicardipine, used for the treatment of hypertension, also have the potential for QT prolongation [25].

It is important to note that patients treated with anti-arrythmic drugs for atrial fibrillation tend to develop TdP soon after conversion to sinus rhythm [3,26].

Non-sedating antihistamines

Second generation antihistamines (H1 inhibitors) were developed mainly to overcome the sedative effect associated with the first generation. QT prolongation and TdP occur most frequently with excessive amounts of terfenadine and astemizol [5,27–29] and is due to potassium channel blockage. QT prolongation with terfenadine is related to accumulation of the parent drug, since terfenadine normally undergoes rapid metabolism by hepatic cytochrome P-450 enzymes (CYP 3A4) to a metabolite that has no effect on potassium channels [29]. A high incidence of TdP with terfenadine treatment was observed in patients with hepatic failure and in those treated concomitantly with drugs that inhibit cytochrome P-450 activity, such as ketoconazole, macrolide antibiotics [27,28] and grapefruit juice [24]. These drugs are contraindicated in patients treated with terfenadine. The drug was withdrawn from use in the USA [3]. In Israel it is still in use under the name TERNALIN®.

TdP was reported in patients who had an overdose of astemizole but also in those who had a modestly increased dose. It is less clear whether co-administration with drugs that block hepatic metabolism of astemizole causes a higher incidence of TdP [27]. Other non-sedating antihistamines are less cardiotoxic. Mizolastine is not metabolized through the liver, and fexofenadine does not block potassium channels. Ceritizine and loratadine block these channels with a lesser potency [24].

Psychiatric drugs

Antipsychotic drugs and antidepressants can cause QT prolongation. The mechanism for this is not fully understood. When taken in therapeutic doses, tricyclic and tetracyclic antidepressants have antimuscarinic effects including sinus tachycardia and shortened RR and QT interval [30]. On the other hand, QT prolongation and TdP have been reported in cases of tricyclic antidepressant overdose [31].

The effects of SSRIs (selective serotonin re-uptake inhibitors) on the cardiovascular system are similar to those of the tricyclic antidepressants (i.e., they usually shorten the repolarization phase) [32]. However, QT prolongation and TdP were reported during treatment with paroxetine [33].

Antipsychotic drugs cause QT prolongation *in vitro* due to Class IA anti-arrhythmic-like action [34]. When given in overdose, thioridazine affects the QT interval more than do the other antipsychotic drugs [35].

Antibiotics

Erythromycin causes QT prolongation and TdP when taken alone, usually by the intravenous route in large doses, or with a second generation antihistamine [36]. There are reports describing QT prolongation during treatment with clarithromycin, and in most of these cases it was taken concomitantly with other drugs that prolong the QT [37].

Clindamycin was reported in association with prolonged QT and resuscitation for ventricular fibrillation [38]. Sparfloxacin caused QT prolongation in 2.4% of 167 patients treated for pneumonia [39] with no documented TdP. Another quinolone that prolongs the QT interval is grepafloxacin, which has been withdrawn from the market [25].

A few case reports have implicated trimethoprim-sulfamethoxazole as a cause of QT prolongation [40]. Pentamidine causes QT prolongation and TdP when given intravenously [41], and recurrent arrhythmia may be present for many days after cession of therapy [42]. Chronic aerosol prophylaxis, on the other hand, does not seem to predispose for QT prolongation [43].

The antimalarial drugs halofantrine [44] and chloroquine prolong QT, usually during intoxication. The effect of chloroquine is probably potentiated through induction of hypokalemia [45]. The antifungal agents ketoconazole, itraconazole and fluconazole interact with other drugs that prolong QT interval (especially terfenadine) through their effect on cytochrome p-450. QT prolongation was also reported when taken alone [28]. The antiviral agent foscarnet can also prolong the QT [25].

Others

Diuretic agents are often reported in association with QT prolongation and TdP. The mechanism facilitating arrhythmia is usually induction of hypokalemia. Indapamide, a thiazide diuretic, can prolong QT independent of potassium levels [46], as can triamterene, a potassium-sparing diuretic [47].

Additional drugs reported in association with QT prolongation and TdP include: probucol, a lipid-lowering drug [48]; ketanserin, a selective serotonin S2 antagonist with alpha-blocking activity [49]; tacrolimus, an immunosuppressive agent [50]; tamoxifen, used in high doses for cancer treatment [25]; terodiline, used for urinary incontinence due to detrusor instability (withdrawn from the market because of this side effect) [51]; clofazimine, an agent for the treatment of leprosy [52]; the somatostatin analogue octeotride [25]; and salmetrol, a sympathomimetic agent for the treatment of asthma [25]. The anticonvulsants falbamate and fosphenytoin [25], the inhalation anesthetic drugs isoflurane and sevoflurane [53], and drugs used for treatment of migraine headaches such as zolmitriptan, sumatripan and naratripan can also cause QT prolongation. The prokinetic agent cisapride was reported in association with TdP when used alone or during treatment with other drugs that interfere with its metabolism through the cytochrome P450 3A4 enzymes [54]. Intoxications with organophosphates [55] and arsenic [56] were reported in association with prolongation of the QT.

The use of liquid protein diets in the 1960s and 1970s was associated with increased risk of sudden death due to TdP [57]. The mechanism was not found and no other formal diet was found to increase the risk, although TdP was documented with significant weight loss in patients with anorexia nervosa [58].

Treatment

Prolonged QT

In patients taking medications with the potential to cause QT prolongation, baseline ECG should be performed with serial ECGs to seek for QT prolongation or other "warning" signs of impending TdP as mentioned above. It is advisable to start treatment with certain medications (especially Class IA and III anti-arrhythmic drugs) during hospitalization, with close monitoring [6,19–21]. The appearance of QT-U changes necessitates withdrawal of the offending drug and correction of any reversible abnormality that contributed to its development. Specifically, potassium levels should be corrected to high normal levels (4.5 mmol/L).

Torsades de pointes

Treatment during the arrhythmia includes drugs aimed at inhibiting the triggered activity and measures to increase basic heart rate.

- Intravenous MgSO4 is considered first line therapy. It is usually given as a 1–2 g bolus. The bolus may be repeated and followed by continuous infusion of 3–10 mg/min, while monitoring for signs of magnesium toxicity (first sign is loss of deep tendon reflexes) [2,11].
- Intravenous lidocain can suppress the arrhythmia in some cases (about 50% response) but its use is controversial [7].
- Intravenous isoproternol 1–4 g/min may increase basic heart rate, but it has the potential to precipitate coronary ischemia in patients with ischemic heart disease and should therefore be used with extreme caution [11]. Its use is also controversial.
- Temporary transvenous pacing also increases basic heart rate and can terminate the arrhythmia. This measure is safe and should be rapidly instituted in TdP that is recurring or not responding to i.v. MgSO4. Pacing rate should be 100–140 beats/min [11].
- Electrolyte abnormalities should be corrected as discussed above.
- In hemodynamically unstable patients (usually because of deterioration into ventricular fibrillation), DC shock should be applied.

Conclusions

Drug-induced prolongation of the QT interval is not an uncommon phenomenon. Physicians treating patients with the drugs discussed above should be aware of their potential to cause life-threatening ventricular arrhythmia. Baseline QT measurements with follow-up serial ECG recordings and QT assessment may be needed in patients treated for prolonged periods with those drugs. Drugs with a high incidence of TdP should be avoided, if possible, in patients with structural heart disease.

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