

Pharmacological and therapeutical basis of torsades de pointes

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ABSTRACT

Torsades de pointes (TdP) is a specific form of polymorphic ventricular tachycardia, which is a dreadful condition, severity varies from mild asymptomatic condition to severe life threatening state. In this review, i would like to highlight the physiological, pathological and pharmacological causes, prevention and management of torsades de pointes. In this present world of therapeutic jungle, due to wide spread use of medication (poly pharmacy), there is a reasonable chance of getting drug interactions resulting in prolonged QTc interval leading to tosades de pointes. The main aim of this study is to bring awareness about risk of developing torsades de pointes in patients receiving multiple drugs and also to make clinicians and pharmacologists little more cautious while prescribing drugs.

Keywords: ECG, QTc interval prolongation, TdP, Arrhythmias, Drugs

INTRODUCTION

Torsades de pointes (TdP) is a specific form of polymorphic ventricular tachycardia characterized by twisting of QRS complexes around the isoelectric line.^{1,2} TdP always follows QT prolongation. TdP is often self-limiting but rapid or prolonged TdP can lead to ventricular fibrillation and sudden cardiac death even in patients with structurally normal hearts. QT prolongation (LQTS) can be either congenital or acquired. Since the withdrawal of cisapride and terfenadine from the market, the drug induced QT prolongation (acquired) leading to TdP has gained importance in the last two decades in the drug development industry.³⁻⁵

History

The French cardiologist Dessertenne coined the term “torsades de pointes”. The word “torsades” refers to an

ornamental motif imitating twisted hairs or threads and “pointes” referred to points or peaks.¹

Epidemiology of torsade de pointes

The prevalence of torsade is unknown. In the United States, 300,000 sudden cardiac deaths occur per year. Torsade probably accounts for fewer than 5%.⁶ For both sexes, the corrected QT interval is longer in white persons than in black persons, possibly explaining the lower susceptibility to acquired torsade in black persons. TdP is 2-3 times more common in women than in men. Women have longer QT intervals and have more QT prolongation secondary to drug therapy.⁷

TdP occurs in patients of a wide age range, from newborns to the very elderly. The highest frequency is in patients aged 35-50 years. TdP that occurs at an early age usually is due to congenital long QT syndrome. In older

persons, it usually is due to acquired long QT syndrome especially drug induced one.

Mechanism of TdP

Ventricular repolarisation phase of cardiac myocytes occur predominantly due to efflux of K⁺ ions. IKr and IKs subtypes of delayed rectifier K⁺ channels are responsible for the efflux. IKr is most susceptible to various drugs and blockade of which results into prolongation of QT interval in ECG subsequently leading to inward depolarisation current (early after depolarisation) promoting triggered activity. The continuation of dispersed repolarisation accompanying the depolarisation may induce re-entry and provoke TdP.^{8,9} Acquired form has a characteristic initiating sequence before the onset of TdP. The first QRS complex of the sequence is usually a ventricular ectopic beat followed by a compensatory pause terminated by a sinus beat which is characterised by a very prolonged QT interval and an exaggerated U wave. When a ventricular extra systole falls on this exaggerated U wave of the sinus beat, it precipitates the onset of TdP. It has been suggested that post-pause accentuation of the U wave may be a better predictor of drug induced TdP than the QT interval (Figure 1 and 2).^{10,11}

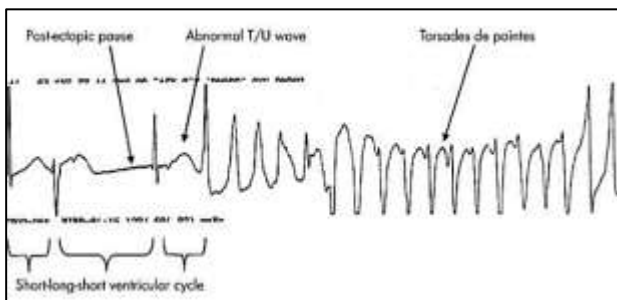


Figure 1: ECG pattern showing abnormal post pause accentuation, abnormal U wave and development of torsedes de pointes.

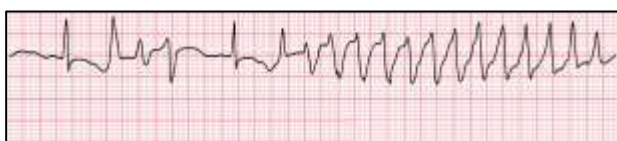


Figure 2: ECG pattern of torsedes de pointes.

Inter-individual differences in susceptibility to QT prolonging drugs have been observed which are possibly due to the genetic variations. Mutations of KCNH2, KCNQ1, KCNE2 and ANKB genes have been identified in some patients with drug induced torsades de pointes of which KCNQ1 mutation is the most common one whose expression results into variability of IKs channel functioning.¹²⁻¹⁴ Furthermore IKs amplitude variability majorly contributes to variability in response to IKr block. More is the IKs amplitude; more is its efficiency to counteract the IKr blocking drugs i.e., QT prolonging

drugs. Factors that increase IKs amplitude are adrenergic stimulation, Endothelin, etc, which increase posttranscriptional upregulation of IKs.¹⁵ Genetically determined reduced activity of cytochrome P450 enzyme CYP3A4 may decrease efficient metabolism of the QT prolonging drugs thioridazine, erythromycin, and terfenadine.¹⁶ Broad area for investigation lies in finding out how the IKs regulates during challenge with an IKr blocker at molecular level.

Measurement of QT interval

It is measured from the beginning of QRS complex to T wave termination representing ventricular depolarization and repolarization and averaged over 3 to 5 beats in a single lead.¹⁷ The QT interval should be measured in either lead II or V5-6. Several successive beats should be measured, with the maximum interval taken. Large U waves (> 1mm) that are fused to the T wave should be included in the measurement. Smaller U waves and those that are separate from the T wave should be excluded. The maximum slope intercept method is used to define the end of the T wave.^{18,19}

More precisely, the risk of TdP is determined by considering both the QT interval and the simultaneous heart rate (i.e. on the same ECG tracing). These values are then plotted on the QT nomogram to determine whether the patient is at risk of TdP. A QT interval-heart rate pair that plots above the line indicates that the patient is at risk of TdP. QTc-prolonging drugs that are associated with a relative tachycardia (e.g. quetiapine) are much less likely to cause TdP than those that are associated with a relative bradycardia (e.g. amisulpride) (Figure 3).

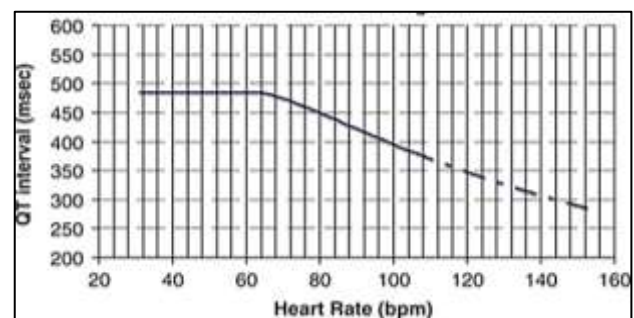


Figure 3: QT interval nomogram.

Normal QT values

QTc is prolonged if >440 ms in men or >460 ms in women; QTc >500 is associated with increased risk of torsades de pointes; QTc is abnormally short if <350 ms.²⁰

Corrected QT

The corrected QT interval (QTc) estimates the QT interval at a heart rate of 60 bpm. This allows comparison

of QT values over time at different heart rates and improves detection of patients at increased risk of arrhythmias. There are multiple formulas used to estimate QTc which include Bazett's formula: $QTc = QT / \sqrt{RR}$; Fredericia's formula: $QTc = QT / RR^{1/3}$; Framingham formula: $QTc = QT + 0.154 (1-RR)$; Hodges formula: $QTc = QT + 1.75 (\text{heart rate}-60)$.²¹

Risk factors of TdP

Hypokalaemia, hypomagnesaemia, hypocalcaemia, hypothermia, bradycardia, myocardial ischemia, post-

cardiac arrest, raised intracranial pressure, congenital long QT syndrome and drugs.²²

Drugs

The list of drugs that can prolong QT interval and/or cause TdP is extensive and concluded either 1) have a risk of TdP, 2) prolong QT and therefore have a possible risk of TdP or 3) have a risk of TdP under certain conditions such as overdose, drug-drug interactions or when administered to certain high-risk individuals (e.g. congenital long QT syndrome) (Table 1).²³⁻³⁶

Table 1: Drugs that can prolong QT interval and subsequent torsades de pointes.

QT interval and subsequent torsades de pointes
Antiarrhythmic drugs:
Type 1 A (TdP reported in all): Quinidine, procainamide, disopyramide
Type 1 C (increase QT by prolonging QRS interval): Encainide, flecainide
Type 3 (TdP reported in all): Amiodarone, sotalol, d-sotalol, bretylium, ibutilide, dofetilide
Calcium channel blockers: Prenylamine, bepridil, terodiline
Psychiatric drugs: Chlorpromazine, droperidol, amitriptyline, nortriptyline, imipramine, desipramine, clomipramine, maprotiline, citalopram, doxepin, fluoxetine, lithium, chloral hydrate, sertindole, pimozide, ziprasidone, thioridazine, haloperidol,
Antihistamines: Terfenadine, astemizole, diphenhydramine, hydroxyzine, ebastine, loratadine, mizolastine
Antimicrobial drugs: Erythromycin, clarithromycin, ketoconazole, pentamidine, quinine, chloroquine, halofantrine, amantadine, sparfloxacin, grepafloxacin, pentavalent antimonial meglumine
Serotonin agonists/antagonists: Ketanserin, cisapride
Immunosuppressant: Tacrolimus
General Anaesthetics: Halothane, isoflurane, sevoflurane
Antidiuretic hormone: Vasopressin
Other agents: Arsenic, adenosine, organophosphates, propracol, papaverine, cocaine
Drug-drug interaction: Pimozide-nefazodone, ranolazine-clarithromycin, quinidine-thioridazine, cisapride-erythromycin, etc.

Prevention of drug induced QT prolongation

Prevention is an important step in the management of drug induced TdP.

Preventive measures include

- Avoid use of QT prolonging drugs in pre-existing heart disease like ventricular arrhythmias and pre-existing electrolyte imbalance
- Do not combine with other QT prolonging drugs
- Do not combine with CYP3A4 inhibitors like ketoconazole, macrolide, etc.
- Do not combine with drugs that cause electrolyte imbalance like diuretics (hypokalemia)
- To be cautious in not exceeding the recommended dose of QT prolonging drug during treatment
- Routine monitoring of ECG is advised before and after the initiation of dose and also when there is need of increase in dosage.

Treatment

The management of acquired LQTS includes the identification and discontinuation of any precipitating drug and the aggressive correction of any metabolic abnormalities, such as hypokalemia or hypomagnesemia. Most of the episodes of TdP are short-lived and terminate spontaneously. Prolonged episodes result in hemodynamic abnormalities which require immediate cardio version. Short-term treatment involves the prevention of recurrence of TdP by administering intravenous magnesium sulfate and temporary transvenous cardiac pacing. Intravenous magnesium is the agent of choice for immediate treatment of TdP irrespective of the serum magnesium level. 2g i.v bolus of magnesium sulfate is followed by intravenous infusion at a rate of 2-4 mg/minute. It probably acts through blockage of sodium or calcium currents. Administration of potassium is an important adjunct to intravenous magnesium for the prevention of TdP, especially in hypokalemia. Serum K⁺ should be maintained in the high

normal range. Lidocaine, isoproterenol, phenytoin, or atropines are reported to be beneficial but their effectiveness is uncertain. Overdrive trans-venous pacing at rates of 90-110 beats/min shortens QTc and is highly effective in preventing recurrences of TdP, especially when they are precipitated by a pause or bradycardia. Cardiac pacing prevents pauses and shortens the QTc interval by enhancing the repolarizing potassium currents. Long-term treatment is rarely required.³⁷⁻⁴⁰

Regulatory perspective in drug development

Apart from antiarrhythmics, many drugs capable of inducing TdP are non-cardiac and are used for relatively benign conditions. Drug regulatory authorities are now concentrating on the identification and if possible quantification of the risk of TdP during the preclinical and clinical development of a drug. Currently there are no contemporary guidelines from regulatory authorities to address this issue. Any adverse event suggestive of cardiac arrhythmias should be reported urgently to drug safety authorities and drug manufacturers. Additional research and development are needed for any compound with the potential to prolong the QT interval.

Summary

It has been well recognized that a prolonged QT interval (congenital or acquired) on ECG is associated with an increased risk of TdP and sudden death. The most common cause of acquired long QT syndrome is drug induced, with antiarrhythmics being the group of drugs most commonly implicated. A large number of non-cardiovascular compounds have been shown to effect cardiac repolarization and to induce proarrhythmias in susceptible individuals. Since the 1990s, seven non-cardiac drugs such as astemizole, terfenadine, cisapride, terodiline, halofantrine, sertindole, and pimozide have attracted regulatory attention because of their propensity to produce QT prolongation, TdP and sudden death. The risk of TdP is likely to remain a significant problem in the future. All the health care giving personnel's and patients should be made aware of this risk and educated accordingly and take precautions to minimize proarrhythmia. Drugs that can prolong the QT interval should ideally be listed and regularly updated in a national drug formulary. Preclinical and clinical evaluations remain the cornerstone for assessing the arrhythmogenic potential of any new drug before approval. Post-marketing surveillance is also important for monitoring spontaneous adverse cardiac effects. Furthermore advances in personal genomics will help in high accuracy prediction of risk of drug induced TdP in the future.

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