

Drug Induced Potential Torsades de Pointes

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Introduction

Torsades de pointes is a form of polymorphic ventricular tachycardia, associated with prolongation of QTc interval, which is life threatening (1). Although found in many clinical settings, the syndrome of torsades de pointes is most often drug induced. Drug induced torsades de pointes is generally accepted as one of the potential adverse outcomes when prescribing anti-arrhythmic drugs for patients with life threatening or incapacitating arrhythmia. Class 1A anti-arrhythmic agents are contraindicated in the treatment of torsoides de pointes and can cause this syndrome. However, it becomes more alarming when it occurs with drugs prescribed for less severe indications, such as antibiotics, antihistamines or neuroleptics.

Causes of Torsades de Pointes

Many conditions may cause prolonged or abnormal repolarisation, if TdP is rapid or prolonged, it can lead to ventricular fibrillation and sudden cardiac death (Fig 1). Essentially, TdP may be caused by either congenital or acquired long QT syndrome (LQTS). In recent years, there has been considerable renewed interest in the assessment and understanding of ventricular repolarisation and TdP. There are several reasons for this. Firstly, the cloning of cardiac ion channels has improved the understanding of the role of ionic channels in mediating cardiac repolarisation, the pathophysiological mechanism of long QTS (congenital and acquired forms), and the pathogenesis of TdP. Secondly, the mutations in genes encoding cardiac ion channels that cause long QT syndrome. Thirdly, there has been considerable enthusiasm for the development and use of class III antiarrhythmic drugs, which prolong repolarisation and cardiac refractoriness. Unfortunately, drugs that alter repolarisation have now been recognized to increase the propensity for TdP. Finally, an increasing number of drugs, especially non-cardiac drugs, have been recognized to delay cardiac repolarisation and to share the ability with class III antiarrhythmic to cause TdP occasionally (2).

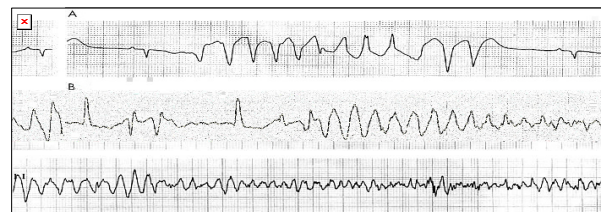


Fig. 1 (A) Self limiting torsades de pointes (TdP)
(B) TdP leading to ventricular fibrillation

Mechanism of action of drug induced QT prolongation and Torsades de pointes

At cellular level, the repolarisation phase of the myocytes is driven predominantly by outward movement of K⁺ ions. A variety of different K⁺ channel subtypes are present in the heart. Two important K⁺ currents participating in ventricular repolarisation are the subtypes of the delayed rectifier, I_{kr} (rapid) and I_{ks} (slow). Blockade of either of these outward K⁺ currents may prolong the action potential. I_{kr} is the most susceptible to pharmacological influence. Blockade of the I_{kr} current manifests clinically as a prolonged QT interval and the prolongation of repolarisation may result in subsequent activation of an inward depolarization current, known as early-after depolarization, which may promote triggered activity. When accompanied by the presence of a notably increased dispersion of repolarisation, this may induce reentry and provoke torsoides de pointes (2) e.g. terfenadine, astemizole).

Since the initial description of torsades de pointes tachyarrhythmia by Dessertenne, many electrophysiologists have been intrigued by the QRS morphological characteristics of arrhythmia, sometimes at the expense of proposing a cohesive electro-physiological mechanism. Dessertenne proposed that the change of QRS axis was due to two competing foci. Several investigators proposed explanations based on shifting circus movement reentry. In reentrant activity in isolated cardiac muscle, a spiral wave of reentrant excitation migrating along the epicardial surface

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could explain the twisting QRS morphology of torsades de pointes. A premature activation wave front arising outside the barrier would propagate along the edge of the column, enter the M region after expiration of its refractoriness, and then reenter at the border to initiate circus movement. Repetition of this type of circus movement with progressively shifting sites of reentry would yield the electrical migration characteristic of torsades de pointes (3).

Table 1. Drugs that can prolong the QT interval (4)

<p>Antiarrhythmic drugs : Azimilide, Bretylium, Clofilium, Dofetilide, Disopyramide, Ibutilide N-acetyl procainamide, Procainamide, Propafenone, Quinidine, Sematilide, DL-sotalol, d-sotalol.</p> <p>Vasodilators/Anti-Ischemic Agents : Bepridil, Lipoflazine, Prenylamine, Papaverine (intracoronary).</p> <p>Psychiatric drugs : Amitryptiline, Clomipramine, Chloral hydrate, Chlorpromazine, Citalopram, Desipramine, Doxepin, Droperidol, Fluphenazine, Haloperidol, Imipramine, Lithium & Maprotiline.</p> <p>Psychiatric drugs : Mesoridazine, Nortryptiline, Pericycline, Pimozide, Prochlorperazine, Sertindole, Sultopride, Thioridazine, Timiperone, Trifluoperazine & Zimeldine.</p> <p>Antimicrobial anti-fungal and antimalarial drugs : Amantadine, Clarythromycin, Chloroquine, Cotrimoxazole, Erythromycin, Grepafloxacin, Halofantrine, Ketoconazole, Pentamidine, Quinine, Spiramycine & Sparfloxacin.</p> <p>Antihistamines : Astemizole, Diphenhydramine, Ebastine, Hydroxyzine & Terfenadine.</p> <p>Miscellaneous drugs : Budipine, Cisapride, Probuocol, Terodiline, Mictuiritin & vasopressin.</p>
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The exact incidence of drug induced TdP in the general population is largely unknown. The awareness of drug induced TdP in the last few years has resulted in an increase in the number of spontaneous reports. The WHO data provide an insight into the incidence of TdP on the most commonly reported pro-arrhythmic drugs (2) (Table 2).

Electrophysiological studies for detecting drug induced effects on repolarisation

Preclinical screening can be conducted in vitro and in vivo using the parent compound, its enantiomers and the major metabolites. Various models should facilitate the testing of this hypothesis for preclinical screening. A number of models having variable advantages and limitations are available (4).

In Vitro Models

(1) Heterologous expression systems

Microinjection of ion channel RNA into *Xenopus laevis* oocytes, Mammalian recombinant expression

Table 2. Twenty most commonly reported drugs associated with torsades de pointes (TdP) between 1983 and 1999

Drug	TdP(n)	Fatal(n)	Total(n)	TdP/total %
Sotalol	130	1	2758	4.71
Cisapride	97	6	6489	1.49
Amiodarone	47	1	13725	0.34
Erythromycin	44	2	24776	0.18
Ibutilide	43	1	173	24.86
Quinidine	33	2	7353	0.45
Terfenadine	41	1	10047	0.41
Clarithromycin	33	0	17448	0.19
Haloperidol	21	6	15431	0.14
Fluoxetine	20	1	70929	0.03
Digoxin	19	0	18925	0.10
Procainamide	19	0	5867	0.32
Terodiline	19	0	2248	0.85
Fluconazole	17	0	5613	0.30
Disopyramide	16	1	3378	0.47
Bepridil	15	0	384	3.91
Furosemide	15	0	15119	0.10
Thioridazine	12	0	6565	0.18
Flecainide	11	2	3747	0.29
Loratidine	11	1	5452	0.20

systems, Human embryonic kidney cells (HEK293), Mouse fibroblasts (C cells) and Chinese hamster ovary (CHO) cells.

(2) Disaggregated cells (studied single or in culture)

(3) Isolated tissues : Dog, Rabbit and guinea pig.

(4) Isolated intact (Langendorff-perfused) heart of guinea pig or rabbit heart studied with electrogram or monophasic action potential recording.

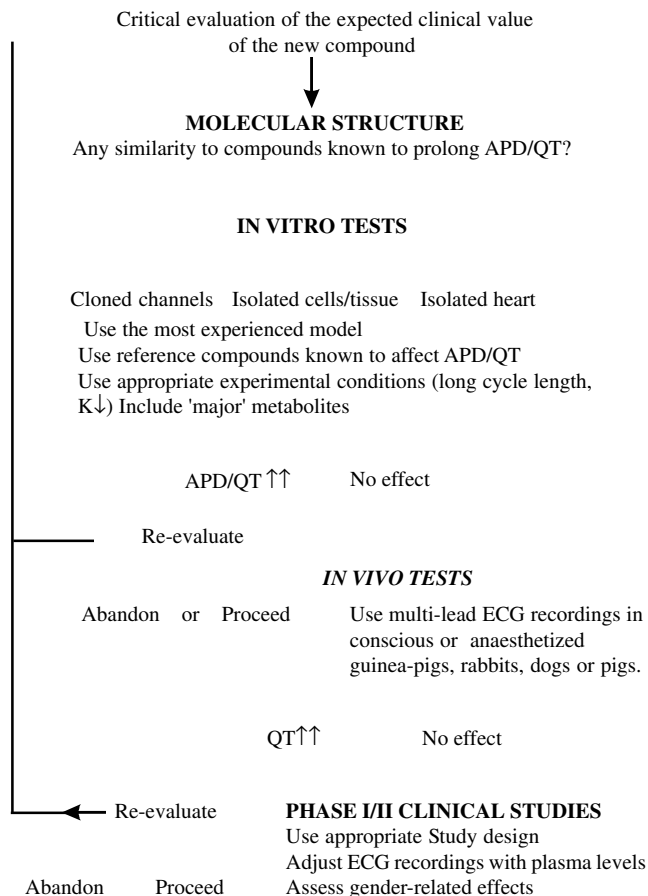
In Vivo Animal Models

(1) Multi-lead ECG recordings in conscious or anaesthetized guinea-pigs, rabbits, dogs or pigs (4,5).

(2) A conscious dog model with TdP-like polymorphic ventricular tachycardia.

(3) A canine model with chronic AV block exposed to d-sotalol. where different pacing modes were used to mimic sequences of short/long/short intervals (6,7).

Following is a proposed flow-chart of studies necessary to assess the potential of drugs to prolong repolarisation on based of above mentioned animal models along with the assessment of preclinical and clinical studies (4).



Antihistamines and Torsades de Pointes

In 1991, FDA expressed concerns about the small but increasing number of reports of serious ventricular arrhythmias associated with antihistamines particularly with non-sedating antihistamines. Second generation antihistamines came into market, in spite of first generation antihistamines available as OTC drugs like diphenhydramine and promethazine. Because of the undesirable side effect of sedation with first generation antihistamines, second generation antihistamines (like terfenadine, astemizole, loratidine, cetirizine, acrivastine, mizolastine, ebastine and fexofenadine) are commonly prescribed and these drugs are not associated with undesirable side effect like sedation. These however, result in various clinical toxicities particularly cardiac toxicity such as terfenadine and astemizole mainly induce QT prolongation and ventricular tachycardia, including torsades de pointes which is life threatening. This potential of both the drugs has raised various questions as to whether

other drugs in this class have similar cardiotoxic potential. But the experimental studies have shown that the ability to cause QTc interval prolongation and the proclivity for producing arrhythmias is not a class effect and is seen only with some second generation non-sedating antihistamines mainly terfenadine and astemizole.

Terfenadine was approved for clinical use in the USA in 1985. At that time, no premonitory CVS events had been associated with its use. In 1989, several cases of cardio toxicity from overdose of terfenadine were reported. Among all about the drug interaction of terfenadine with inhibitors of CYP-450 oxidative pathways, a study confirmed that erythromycin alters the metabolism of terfenadine, leading to terfenadine accumulation and, consequently, altered cardiac repolarisation (8).

Furthermore, similar adverse events had been reported with the use of astemizole. Since its approval in 1988, 44 similar serious cardiovascular events had been reported through mid-1992. The reports included 23 cases of torsades de pointes, 10 cases of ventricular tachycardia, 9 cardiac arrests, and 5 cardiovascular deaths. Most of the cases occurred in patients overdosed with astemizole. Torsades de pointes occurred in two patients who reported taking the normally prescribed doses of 10 or 20 mg daily (8).

Drug Interactions and Torsades de pointes (9, 10)

Drug interactions with non-sedating antihistamines, terfenadine and astemizole are metabolized by the CYP3A subfamily, and drug interactions resulting in an accumulation of these drugs have been associated with torsades de pointes, a life-threatening cardiac arrhythmia characterized by altered cardiac repolarization and a prolonged QTc interval. Terfenadine undergoes virtually complete first-pass elimination (>99%) to an inactive metabolite. Similar for astemizole in that substantial first-pass metabolism occurs and active metabolites are formed. For both terfenadine and astemizole, it is the parent compound, not the metabolites, which are cardiotoxic.

Some of the initial interactions of nonsedating antihistamines (resulting in torsades de pointes) occurred with the systemic antifungal agents. Both ketoconazole and fluconazole inhibit CYP3A, but of the two, only

ketoconazole has been associated with terfenadine-induced ventricular arrhythmias. Although fluconazole causes inhibition of CYP3A *in vitro*, co administration of fluconazole and terfenadine does not result in clinically significant cardiovascular adverse events or an increase in plasma terfenadine level at a fluconazole dose of 200 mg per day. Fluconazole also does not appear to interact with astemizole in a clinically significant manner. Pharmacists should be aware, therefore, that the possibility of an interaction between fluconazole and a nonsedating antihistamine in a given individual cannot be ruled out depending on the fluconazole dose administered and the presence of risk factors for drug-induced torsades de pointes, such as coronary artery disease, preexisting prolonged QT interval, hypokalemia or concurrent use of drugs that prolong the QT interval—such as amiodarone, sotalol, quinidine or thioridazine. The available evidence suggests that itraconazole should not be administered with terfenadine or astemizole because of its ability to inhibit CYP3A is of the same magnitude as that of ketoconazole. The new antifungal terbinafine does not appear to inhibit CYP3A to a clinically significant extent. Studies show that ketoconazole, erythromycin and cimetidine can inhibit the metabolism of loratadine and its metabolite descarboethoxyloratadine (DCL), but these interactions appear to be of little clinical significance because neither ECG abnormalities nor other adverse events were observed as a result of the increased plasma concentrations of DCL. Loratadine does not, therefore, appear to be cardiotoxic. The macrolide antibiotics are also inhibitors of CYP3A, as previously discussed. Azithromycin does not appear to inhibit terfenadine metabolism to a significant extent, in contrast to erythromycin and clarithromycin. In addition toazole antifungals and macrolide antibiotics, several selective serotonin reuptake inhibitor (SSRI) antidepressants inhibit the CYP3A subfamily, but to a lesser extent. Though the data are not as clear in the case of the SSRIs as for the antifungals and macrolides, several case reports have suggested that they may also predispose a patient to the development of life-threatening arrhythmias.

Another inhibitor of CYP3A, and thus of nonsedating antihistamine metabolism, is quinine. Quinine, at doses greater than 430 mg/day, is contraindicated for use with astemizole because elevated plasma

concentrations of both astemizole and its metabolite, desmethylastemizole, accompanied by QT prolongation, have occurred with concurrent use. Tonic water, which contains quinine, can elevate the plasma levels of astemizole and its metabolite. At amounts of less than 32 oz. of tonic water (80 mg of quinine), this effect is small and is not accompanied by significant prolongation of the QT interval. Until more information is available, it would also be prudent to limit the dose of quinine and tonic water in patients taking terfenadine or astemizole.

Another beverage that can inhibit CYP3A is grapefruit juice. This is thought to be due to one or more components in the grapefruit juice. The metabolism of terfenadine has been shown to be altered in patients receiving grapefruit juice. Thus, pharmacists should caution patients taking astemizole or terfenadine, not to take their medicine with grapefruit juice. Other fruit juices do not appear to bring about this effect.

Prevention of Drug Induced QT Prolongation (2)

In clinical practice, adverse effects of QT prolonging drugs can be prevented by not exceeding the recommended dose, avoiding their use in patients with pre-existing heart disease or risk factors as mentioned above, previous ventricular arrhythmias, and/or electrolyte imbalance such as hypokalemia. Concomitant administration of drugs that inhibit the cytochrome P450 (imidazole antifungals, macrolide antibiotics and grape juice) or those that can prolong the QT interval or drugs that cause electrolyte disturbance should be avoided. The serum potassium concentration should be checked regularly as a matter of routine care when the patient is on potassium wasting diuretics. Furthermore, it may be sound clinical practice to perform ECG routinely before and after initiation or increment of dosage of a drug that may prolong the QT interval. If the patient develops TdP, the offending drug should be stopped and electrolyte abnormalities corrected. Drugs that can prolong the QT interval should really be listed and regularly updated in a national drug formulary, which is not the case in present. Any adverse events suggestive of cardiac arrhythmias should be reported urgently to drug safety authorities and/or drug manufacturers. The management of patients with drug induced TdP includes identifying and withdrawing the offending drug(s), replenishing the

potassium concentration to 4.5-5 mmol/L, and infusing intravenous magnesium (1-2 g). In resistant cases, temporary cardiac pacing may be needed to increase the heart rate and shorten the QT interval.

Regulatory perspective in drug development (2)

Apart from anti-arrhythmics, many drugs capable of inducing TdP are non-cardiac and are used for relatively benign conditions. Regulatory authorities in the European Union (EU) are now concerned that the risk should be identified and if possible quantified during the preclinical and clinical development of a drug. Currently there are no contemporary guidelines from other regulatory authorities to address this issue. In 1997, the UK Committee for Proprietary Medicinal Products (CPMP) adopted a document entitled Points to consider: the assessment of the potential for QT interval prolongation by non-cardiovascular medicinal products. The CPMP guideline document should be viewed as a strong signal from the public health authorities that the problem of QT prolongation, especially by non-cardiac drugs, is significant and requires careful scrutiny. Additional research and development are needed for any compound with the potential to prolong the QT interval. The CPMP document details the necessary preclinical and clinical stages required for testing the safety of new active substances.

Conclusions

Terfenadine and astemizole may induce QT interval prolongation and ventricular arrhythmias, including torsades de pointes, in some patients in the following clinical settings: (1) over dosage; (2) concomitant administration of ketoconazole; (3) concomitant administration of erythromycin or macrolide antibiotics; (4) significant hepatic dysfunction; (5) preexisting cardiovascular disease. The existence of these risk factors and the widespread use of these drugs are elements that may explain the higher incidence of torsades de pointes than would have been expected otherwise. Nevertheless, as they are widely prescribed for a self-limiting, non-fatal disease, the risk

attributable must be assessed very carefully. The FDA and the manufacturers of terfenadine and astemizole have attempted to address these issues by identifying the subpopulations of patients at risk of torsades de pointes and announcing warnings in product labels, "Dear Doctor" letters, and various professional journals. Currently, these drugs are available in the U.S. by prescription only. The FDA considers terfenadine and astemizole to be safe and effective drugs when used properly.

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