

A Case Series of Drug-Induced Long QT Syndrome and Torsade de Pointes

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ABSTRACT

Introduction: Torsade de Pointes (Tdp) is a form of polymorphic ventricular tachycardia in the setting of prolonged QT interval. Any drug that prolongs repolarisation, and hence QT interval, may cause Tdp. Predisposing factors of drug-induced Tdp include female sex, bradyarrhythmia and hypokalaemia.

Methods: We retrospectively analysed the casenotes of 13 patients with drug-induced LQTS from 1991 to 2000 from National Heart Centre and Changi General Hospital.

Results: Causative drugs in the series were amiodarone (seven patients, 54%), sotalol (two patients), quinidine (one patient), phenothiazine (two patients) and astemizole (one patient). There were eight females and all were Chinese. The mean age was $72 \pm$ nine years. The patients commonly present with syncope (38%) and cardiac arrest (38%). The mean corrected QTC interval was 545 ms. The most common precipitating factor was hypokalaemia (31%). Nine patients require cardiopulmonary resuscitation and two patients (15%) died. Nine patients (69%) had underlying structural heart disease such as ischaemic heart disease, valvular heart disease and hypertensive heart disease. The left ventricular ejection fraction was normal in six patients. The onset of Tdp ranged from Day 2 to Day 5 in the seven patient with amiodarone-induced LQTS. These were inpatients who were given intravenous loading doses of amiodarone. Both patients with sotalol-induced LQTS were females on sotalol 80 mg and 240 mg per day with Tdp occurring on Day 2 and 10 months respectively.

Conclusion: Tdp is a potentially life-threatening arrhythmia. The list of torsadogenic drugs is ever expanding. Physicians need to know the drugs which can lead to Tdp. Careful assessment of risk-benefit ratio is important before prescribing such drugs. Amiodarone-induced Tdp is not uncommon in

our local population. Initiation of a class III agent, especially amiodarone, should be done judiciously, with monitoring of the QT interval and avoidance of hypokalaemia.

Keywords: drug-induced long-QT syndrome, Torsade de Pointes, class III agent, torsadogenic drugs

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INTRODUCTION

Torsade de Pointes (Tdp) is a form of polymorphic ventricular tachycardia, characterised by QRS complexes of alternating polarity that appears to twist around the isoelectric line, and occurs in the setting of prolonged QT interval. It is the classic form of proarrhythmia from drugs that prolong the QT interval. LQTS is either congenital or acquired. The list of drug-induced LQTS is continuously expanding. Any drug that prolongs repolarisation, and hence the QT interval may be proarrhythmic. We report here a series of 13 cases of drug-induced LQTS.

METHOD

We retrospectively analysed the casenotes of 13 patients with drug-induced LQTS from 1991 to 2000 from National Heart Centre and Changi General Hospital.

RESULTS

There were 13 patients; eight patients were female (62%) and all were Chinese. The mean age was $72 \pm$ 9 years, ranging from 61 years to 88 years.

The causative drugs in the series were amiodarone (seven patients, 54%), sotalol (two patients), phenothiazines (two patients), quinidine (one patient) and astemizole (one patient). The common presentations were syncope (38%) and cardiac arrest (38%). One patient (Patient 10) presented with focal seizure collapsing from cardiac arrest. Another patient (Patient 6) was asymptomatic. Nine patients (69%) required cardiopulmonary resuscitations. There were two deaths. The most common precipitating factor was hypokalaemia (31%).

The underlying cardiac disease varies (Table I). The left ventricular ejection fraction was normal in six out

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Table I. Summary of patients with drug-induced long QT syndrome.

Pt	Age (yrs)	Sex	Drug	Cardiac Disease	LVEF	QTC Interval (ms)	Presentation	Predisposing Factor	Outcome
1	66	M	Amiodarone	DCMP	25%	550	Syncope	Hypokalaemia	Survived
2	77	F	Amiodarone	DCMP	30%	460	Cardiac Arrest		Died
3	87	F	Amiodarone	SSS	50%	708	Cardiac Arrest	Hypokalaemia Flecainide	Stroke PPM
4	84	F	Amiodarone	DCMP	35%	451	Syncope		AVNA PPM
5	73	F	Amiodarone	NK	NK	614	Cardiac Arrest	Junctional Brady Diltiazem	AVNA PPM
6	76	M	Amiodarone	IHD	30%	524	Asymptomatic		Survived
7	61	M	Amiodarone	MVP	62%	455	Syncope		Died
8	67	F	Sotalol	RHD	65%	544	Syncope	Hypokalaemia	ANA PPM
9	88	F	Sotalol	IHD	65%	620	Dyspnoea		Survived
10	67	M	Phenothiazine	HHD	60%	485	Seizure		Survived
11	65	F	Phenothiazine	NK	60%	539	Cardiac Arrest	Hypokalaemia	Survived
12	61	M	Quinidine	IHD	50%	NK	Cardiac Arrest		Survived
13	67	F	Astemizole	NK	NK	594	Syncope		Survived

DCMP = dilated cardiomyopathy; SSS = sick sinus syndrome; RHD = rheumatic heart disease; IHD = ischaemic heart disease; MVP = mitral valve prolapse; NK = not known; PPM = permanent pacemaker; AVNA = AV nodal ablation.

of the 10 patients who had echocardiography done. The mean corrected QT interval was 545 ms (based on Bazett's formula). Tdp was documented in all patients.

Amiodarone-induced LQTS and Tdp occurred in seven patients. Four of the patients were female. The mean age was 74 years. The two deaths in this series occurred in this group. The mean corrected QT interval for this group of patients was 534 ms (range 451 ms to 708 ms). The onset of Tdp ranged from Day 2 to Day 5 after initiation of amiodarone. All were given intravenous loading doses of amiodarone. The most common indication for using amiodarone was for the control of ventricular rate in atrial fibrillation (five patients). Patient 7 was given amiodarone for the control of ventricular tachycardia and patient 5 was on amiodarone for multifocal atrial tachycardia. Five patients (71%) had underlying structural heart disease, out of which four patients had severe to moderate impairment of left ventricular function.

Patient 1 and 2 had dilated cardiomyopathy and atrial fibrillation with fast ventricular rate. Both developed Tdp on Day 4 and seven respectively. Patient 2 became asystolic rapidly and died despite resuscitation. Patient 3 was given sotalol 160 mg bd followed by flecainide 100 mg bd for pharmacological cardioversion of atrial fibrillation. When she failed electrical cardioversion, intravenous amiodarone was started. Her QTC was 520 ms before amiodarone and

it increased to 708ms after amiodarone. She was haemodynamically unstable during Tdp and required DC shock. Although she survived, she suffered a left frontal stroke. Patient 4 and 5 required AV nodal ablation for incessant atrial fibrillation with VVI pacemaker insertion. Patient 5 developed junctional bradycardia after diltiazem was added to amiodarone for control of ventricular rate in atrial fibrillation. This precipitated her into Tdp. Patient six, who was on amiodarone for multifocal ventricular ectopics, showed gradual prolongation of QT interval and developed sustained Tdp captured on 24-hour Holter monitoring. He was asymptomatic during the arrhythmia. Patient 7 presented with recurrent syncope corresponding to runs of ventricular tachycardia. When lignocaine failed to control the ventricular tachycardia, intravenous amiodarone was added on. The next day, he developed Tdp and went into incessant ventricular tachycardia and ventricular fibrillation and died.

Sotalol-induced LQTS and Tdp occurred in two females (Patients 8 and 9). The dosages of sotalol used were 240 mg and 160 mg for Patients 8 and 9 respectively. The corrected QT interval were 544 ms and 620 ms respectively. Both had normal serum creatinine. Patient 8 had underlying rheumatic heart disease of mitral stenosis and moderate mitral regurgitation on anticoagulation for chronic atrial fibrillation. She was on sotalol 120 mg bd for 10 months

Table II. List of torsadogenic drugs.

Antiarrhythmic drugs	
Class I	quinidine, disopyramide, procainamide
Class III	sotalol, amiodarone
Non-antiarrhythmic drugs	
Antibiotic	erythromycin, bactrim
Antifungal	ketoconazole, itraconazole
Antihistamine	terfenadine, astemizole
Psychiatric drugs	tricyclic antidepressants, phenothiazines, haloperidol
Cholinergic antagonists	cisapride, organophosphates
Other drugs	cocaine, arsenic

before she developed Tdp which was precipitated by hypokalaemia (serum potassium = 2.9 mmol/l) from diuretic therapy.

Patient 12 had quinidine-induced LQTS. This patient had been on quinidine 1200 mg/day and digoxin 0.0625 mg for atrial fibrillation. Two weeks later, he presented at the accident and emergency department in cardiac arrest from ventricular tachycardia which degenerated into ventricular fibrillation. ECG showed prolonged QT interval. He was cardioverted, started on intravenous lignocaine infusion and quinidine was stopped. The QT interval normalised and there was no recurrence of Tdp.

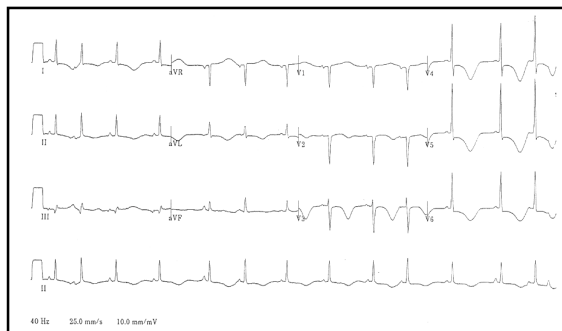
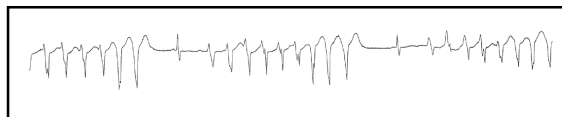
Patients 10 and 11 were on phenothiazine 100 mg/day respectively for schizophrenia. The duration of therapy was indeterminate. They had prolonged QT interval and Tdp which degenerated into ventricular fibrillation in Patient 11. Both survived.

Patient 13 was noted to be on astemizole (dosage not recorded) for "a few weeks" for an upper respiratory tract infection. She presented with syncope and head injury with a left parietal haematoma. She was found to have prolonged QTC interval of 594 ms and T wave alternans. There was non-sustained Tdp on admission.

DISCUSSION

Tdp is an idiosyncratic proarrhythmic reaction to antiarrhythmic drugs. Drugs that prolong the QT interval are known for their potential to provoke Tdp. The list of drugs that induced Tdp is expanding. It commonly produces syncope, but can be occasionally asymptomatic initially. It is life threatening when sustained or when it degenerates into ventricular fibrillation.

The onset of Tdp varies. Half of the patients will develop Tdp within several days of initiation, while the others will develop it after several months or years of therapy. This late occurrence is either due to a change

**ECG I** Prolonged QT interval from amiodarone (542 ms).**ECG 2** Torsade de Pointes.

in drug dose, or the introduction of predisposing factor such as hypokalaemia or bradycardia. Patient 8 who was asymptomatic on sotalol for 10 months until she developed hypokalaemia illustrated this. The risk of Tdp varies with different drugs and is not quantitatively related to the degree of QT prolongation. Electrocardiographic warning signs include bradycardia, very prolonged QT interval (<600 ms), appearance of prominent U waves, extrasystoles, and U wave augmentation after extrasystole.

Antiarrhythmics, particularly the Class I and Class III agents, are potentially proarrhythmic. Tdp is the specific form of proarrhythmic action of these drugs. Amiodarone is a complex drug with both Class I and Class III action approved by the Food and Drug Administration for sustained ventricular tachycardia⁽¹⁴⁾. It is being used increasingly for atrial fibrillation, either as an attempt for pharmacological cardioversion or control of ventricular rate, as reflected in this paper. Despite substantial QT prolongation (by about 20%) and bradycardia, the proarrhythmic risk with amiodarone is reportedly low (<1%)⁽¹⁾, even in the setting of poor ventricular function. It is difficult to predict the occurrence of Tdp with amiodarone. Although not quantitatively correlated, it is suggested that if QT interval exceeds 600 ms, amiodarone should be discontinued. It is also advisable to watch for hypokalaemia, especially during initiation of diuretic therapy, and to avoid the combination of drugs which may further aggravate bradycardia (such as in Patient 5).

Although purportedly uncommon, the incidence of amiodarone-induced Tdp in the Asian population is unknown. The potentially life-threatening outcome of Tdp warrants judicious use of amiodarone and frequent monitoring. Both deaths in this series were due to amiodarone-induced Tdp.

Sotalol is a racemic mixture of d- and l-isomers. The incidence of Tdp with d- and l-sotalol is about 4%. Tdp had been documented in patients on d-sotalol as well^(3,5,12). Clinical variables that correlate with the risk of Tdp from sotalol are female sex, a presenting arrhythmia of sustained VT or VF, d, l-sotalol dosage of >320 mg/day, history of congestive cardiac failure and high serum creatinine. Women had a threefold greater chance of developing Tdp than men⁽⁷⁾. Both patients had risk factors such as female gender and congestive cardiac failure. Furthermore, Patient 9 presented with sustained VT. However, they were on dosages less than 320 mg/day.

The estimated frequency of Tdp during quinidine therapy ranges from 2% to 8%^(5,8). The use of quinidine, as well as other class IA antiarrhythmics, is uncommon in current clinical practice.

Non-antiarrhythmic drugs such as the non-sedating H1 antagonist, psychiatric drugs and antibiotics may prove Tdp⁽⁵⁾. Tdp from these drugs is usually due to increased serum drug concentrations. The three major reasons for the increase plasma levels are intentional drug overdose, a decrease in metabolism due to liver disease or a drug to drug interaction⁽¹³⁾. The published literature on astemizole-induced Tdp consists of case reports of astemizole overdose, with dose ranging from 20 mg to 300 mg. The recommended daily dose is 10 mg. Drug interaction between antifungal drugs and macrolide antibiotics, eg ketoconazole and erythromycin, which are metabolised by the same cytochrome P450 3A4 hepatic isoenzyme, can cause LQTS and Tdp.

Treatment of drug-induced Tdp requires identification of the arrhythmia, cessation of the culprit drug and correction of predisposing factors. Emergency therapy includes DC shock if it degenerates into ventricular fibrillation, intravenous magnesium sulphate and acceleration of heart rate with transvenous cardiac pacing or isoproterenol⁽¹⁻⁶⁾. Lignocaine is useful only in about 50% of cases of Tdp.

The aim of accelerating the heart rate in Tdp is to shorten the delayed repolarisation duration. Pacing rates of 100 - 140 beats per min may be necessary initially and then tailed down gradually till the QT interval normalises and ventricular ectopics subside. Isoproterenol is contraindicated in patients with hypertension and coronary artery disease. It should be considered only if cardiac pacing cannot be started immediately, presence of underlying bradycardia, if Tdp is pause-dependant and is definitely caused by acquired LQTS.

Evidence suggests that patients with acquired LQTS may be genetically predisposed to Tdp. Carriers of LQT-gene can have normal QT interval and remain symptom-free until exposure to torsadogenic drugs.

Silent gene carriers have been identified in patients with drug-induced Tdp and in their relatives. Thus, identification of LQTS (congenital or acquired) should prompt counselling of patients and relatives about the increased risk from medications.

LIMITATIONS

The possibility of ischaemic heart disease as a compounding factor for the development of Tdp in this elderly group of patients cannot be entirely ruled out, particularly in Patients 1, 2, 4 and 7 who were given amiodarone. However, the chronological sequence of events with the resolution of prolonged QT interval after withdrawal of offending drugs and the absence of other symptoms or signs of ischaemia point to the high probability of drug-induced Tdp.

CONCLUSIONS

Drug-induced Tdp is a potentially life-threatening arrhythmia. Care must be taken to minimise the risk of proarrhythmia from drugs. Physicians and patients should be aware of the expanding list of torsadogenic drugs and the possibility of inducing Tdp from drug interactions. Careful assessment of risk-benefit ratio is important before initiating such drugs.

Risk factors for drug-induced Tdp include female sex, hypokalaemia, bradyarrhythmia, congestive cardiac failure, impaired ejection fraction and a history of drug-induced Tdp. Class III agents such as amiodarone and sotalol should be initiated judiciously in such patients with close monitoring of the QT interval and serum potassium level. Counselling of patients with drug-induced Tdp and their relatives about the increased risk of Tdp from torsadogenic drugs is necessary.

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