Pharmacological treatment of acquired QT prolongation and torsades de pointes

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ABSTRACT

Torsades de pointes is a characteristic polymorphic ventricular arrhythmia associated with delayed ventricular repolarisation as evidenced on the surface electrocardiogram by QT interval prolongation. It typically occurs in self-limiting bursts, causing dizziness and syncope, but may occasionally progress to ventricular fibrillation and sudden death. Acquired long QT syndromes are mainly caused by cardiac disease, electrolyte abnormalities or exposure to drugs that block rectifying potassium channels, especially IKr.

Management of torsades de pointes or marked QT prolongation includes removal or correction of precipitants, including discontinuation of culprit drugs, and institution of cardiac monitoring. Electrolyte abnormalities and hypoxia should be corrected, with potassium concentrations maintained in the high-normal range. Immediate treatment of torsades de pointes is by intravenous administration of magnesium sulphate, terminating prolonged episodes using electrical cardioversion. In refractory cases of recurrent torsades, the arrhythmia can be suppressed by increasing the underlying heart rate using isoproterenol or transvenous pacing. Other interventions are rarely needed, but there are case reports of successful use of lidocaine or phenytoin. Antiarrhythmic drugs that prolong ventricular repolarisation should be avoided.

Some episodes of torsades de points could be avoided by careful prescribing of QT prolonging drugs, including an individualised assessment of risks and benefits before use, performing baseline and periodic electrocardiograms and measurement of electrolytes, especially during acute illnesses, using the lowest effective dose for the shortest possible time and avoiding potential drug interactions. These steps are particularly important in those with underlying repolarisation abnormalities and those who have previously experienced drug-induced torsades.

BACKGROUND

It is now half a century since the French cardiologist François Dessertenne published his original report of a characteristic polymorphic ventricular tachycardia and coined the phrase 'torsades de pointes'[a] (TdP) or 'twisting of the points' to describe its ECG appearance.(1) This uncommon arrhythmia characteristically occurs in self-terminating bursts, causing dizziness or syncope and occasionally convulsions, but can occasionally degenerate into ventricular fibrillation, resulting in sudden cardiac death.

Torsades occurs when there is delayed ventricular repolarisation with associated triggered activity due to early afterdepolarisations (EADs). Drug-induced delayed repolarisation characteristically occurs because of blockade of rectifying potassium channels and is reflected on the 12 lead ECG by prolongation of the QT, which almost invariably precedes torsades. EADs occur because of continuing late calcium entry resulting from delayed inactivation of voltage-gated calcium channels as a consequence of prolonged ventricular depolarisation.

The QT interval

The QT interval extends from the onset of the QRS complex to the end of the T wave and reflects the duration of ventricular depolarisation and repolarisation. Factors that affect depolarisation, such as sodium channel blockade, may prolong the QT interval as a result of increases in QRS duration. The majority of the QT interval, however, from the J point to the end of the T wave (the JT interval), reflects ventricular repolarisation and the QT interval is more sensitive to factors that influence this component.

Prolongation of the QT interval can be congenital (genetic) or acquired. Congenital long QT syndromes (cLQTS), not considered in detail in this article, are caused by genetic loss-of-

[a] The correct orthography is disputed, with several variations used in the literature (including by French authors). These include *torsades des pointes, torsade de pointes*, etc. This article uses Dessertenne's original form - *torsades de pointes.*

function mutations that affect the rectifying potassium channels primarily responsible for cardiac repolarisation, such as IKr, IKs or IK1, or gain-of-function mutations affecting sodium or rarely L-type calcium channels.(2) Acquired LQTS (aLQTS) is caused by heart disease, electrolyte abnormalities and/or exposure to precipitating ('culprit') medications, of which a large number have been implicated (Table 1). These drugs usually delay cardiac repolarisation by blocking relevant potassium channels, especially IKr, which is encoded by the gene previously referred to as HERG (the human ether a go go-related gene) but now termed *KCNH2*. The risk of torsades with individual drugs is often not well defined, but is generally higher for most antiarrhythmic agents (e.g. quinidine, sotalol) than non cardiovascular drugs; amiodarone is thought to be an exception, carrying a low risk of TdP. Antiarrhythmics are also used in patients likely to have other risk factors.

Assessing risk

The extent of QT prolongation is one of several important risk factors for the development of torsades. Clinical use of the QT interval as a biomarker for risk of TdP is, however, hampered by practical difficulties in measurement in a clinical context. While many modern ECG machines provide automated measurements of QT interval upon which many clinicians rely, (3) these are not always accurate, so manual confirmation is essential, especially when the ECG is abnormal. Manual measurements are, however, often problematic due to uncertainty over the end of the T wave, especially in patients with repolarization abnormalities and/or prominent U waves. Indeed variability of measurement amongst cardiologists and even cardiac electrophysiologists can be worryingly high.(4)

It is also necessary to take account of the heart rate, because the QT interval shortens as heart rate increases. Although TdP due to aLQTS is uncommon in patients with tachycardia, accurate assessment of delayed repolarisation is still important because of the risk of TdP in the event of subsequent bradycardia or pauses. Various formulae are available to provide a QT interval corrected to a heart rate of 60/min (QTc). The original and still most commonly

used formula is that of Bazett ($QTc = QT/[RR^{0.5}]$),(5) but a major limitation is that this over-corrects the QT interval in patients with tachycardia resulting in spurious apparent QTc prolongation, with the reverse occurring in those with bradycardia. These effects are less marked with more sophisticated correction formulae such as the Fridericia ($QTc = QT/[RR^{0.33}]$) or Framingham [$QTc = QT + 0.154(1-RR)$] methods.(6) All these formulae, however, require calculation based on the RR interval and even if the measurement of QT interval is accurate, this is challenging in a clinical environment. Also, because of individual variation in the relationship between heart rate and QT interval,(7) no universal formula will provide an ideal heart rate correction for a specific patient.

Women have, on average, longer QT intervals than men, a difference that emerges around puberty, and are at higher risk of TdP. Using the Bazett formula, a QTc greater than 450 ms in a male and 470 ms in a female is considered abnormal in adults.(6, 8) More recently it has been suggested that the 99th centiles for otherwise healthy adults are used as limits of normality, 470 ms for males and 480 ms for females.(9) TdP is unusual if the Bazett-QTc is less than 500 ms, although can occur, especially in those with bradycardia; heart rate correction is therefore probably unnecessary in those with heart rates below 60 /min. In one study the average QT and Bazett-QTc intervals preceding drug-induced torsades were 580 and 590 ms respectively. (10)

More recently a heart rate-QT interval nomogram has been described for risk stratification (Figure 1). This method is attractive because avoids the need for correction formulae and is based on heart rate rather than RR interval. Because the relationship between QT interval, heart rate and risk is uncertain in those with more rapid heart rates, an interrupted nomogram line is used for heart rates above 105 /min. As well as being simple to use, the heart rate-QT nomogram separates patients who develop TdP from those who do not with improved sensitivity and specificity compared to the various heart rate correction formulae described above. (11)

The QT interval is just one important determinant of the risk of TdP and other risk factors should also be taken into account when planning patient management. In aLQTS the arrhythmia is more likely to occur in those with bradycardias or pauses because impairment of IKr produces a prolonged and often dispersed or variable repolarisation. Ventricular premature contractions may increase risk because they are associated with compensatory pauses that predispose to TdP. They may result from early after depolarisations (EADs) occurring above a certain threshold required to cause triggered activity that can induce arrhythmia. The arrhythmia is more likely to develop if there is instability of repolarisation as reflected on the ECG by T/U wave variability, such as T wave alternans or short term variations in the QT interval. (9, 12) TdP is more common in those with structural heart diseases, including heart failure, myocardial infarction and left ventricular hypertrophy, as well as those with cLQTS, which may be concealed. Other risk factors include advanced age, female sex, alcoholic liver disease, recent conversion from atrial fibrillation, hypokalaemia, hypomagnesaemia, hypocalcaemia and digoxin or diuretic therapy. High concentrations or rapid intravenous infusion rates of a QT-prolonging drug increase risk, such as following overdose or when there is reduced drug elimination due to liver or renal impairment.(9, 13, 14)

Typically, development of severe QT prolongation or torsades requires several precipitating factors to occur in combination, to overcome a ‘repolarisation reserve’ generated by the presence of multiple rectifying potassium channels.(9) Precipitants of aLQTS exacerbate repolarisation delay in those with cLQTS, while genetic mutations affecting relevant cardiac channels have been identified in a proportion of patients with aLQTS.(15, 16) Common genetic variation may also predispose to aLQTS but investigation has so far proven either limited or disappointing.(17) Patients receiving culprit drug therapies may remain well and have a normal ECG until other factors supervene such as electrolyte abnormalities, bradycardias or pauses, when QT prolongation and TdP may develop (‘late proarrhythmia’).

Prevention of torsades de pointes

Over the past three decades drug regulatory authorities have taken steps to reduce the risk of licensed medicines causing TdP and this has resulted in several drugs being removed from the market or use severely restricted. Drug development now requires detailed assessment of the electrophysiological effects of new drugs and, unless justification can be provided, human studies assessing effects on the QT interval.(6) This makes it less likely that unexpected TdP will occur after drugs are marketed, such as occurred previously for several drugs such as probucol, terfenadine, astemizole, grepafloxacin, thioridazine and cisapride. It does however increase the cost of drug development and the chance of late failure of a novel drug to proceed to market.

Many episodes of TdP might be avoided by more skilful prescribing and monitoring of QT prolonging therapy. The benefit-risk balance of drug use should be considered on an individualised basis, taking into account the patient's medical history, baseline ECG and blood test results. This is challenging for prescribers as the risks associated with such patient factors are not clearly defined. When a QT prolonging drug is needed, the lowest effective dose should be used and the drug should be discontinued when no longer required. It may be difficult for prescribers to find information about the propensity of drugs to prolong the QT interval or cause TdP, but frequently updated information is available, for example from the CredibleMeds website.(18)

Drug interactions are important precipitants of torsades and avoiding these is essential. These may be pharmacokinetic, for example via inhibition of metabolism (Table 2), or pharmacodynamic, where for example two QT prolonging drugs are used together. There are numerous clinical examples of TdP occurring after interactions of both main categories. (19)

It is important to have access to an ECG in all patients receiving drugs that may prolong the QT interval. Depending upon the clinical and individual circumstances and the risk

associated with the drug being used, it may be appropriate to perform baseline ECGs and blood tests before prescribing and repeating these after dose increases, with co-prescription of drugs that may interact or during times of intercurrent illness. Useful advice on risks and the need for ECG monitoring may be found in the drug's summary of product characteristics. Monitoring potassium, magnesium and calcium concentrations is particularly important if there are clinical reasons for concern, for example with gastrointestinal disturbances or institution of diuretic therapy.

MANAGEMENT

The American College of Cardiology (ACC), American Heart Association (AHA) and European Society for Cardiology ESC) published guidelines for management of ventricular arrhythmias, including drug-induced TdP, in 2006.(20) and the key recommendations have been endorsed in a more recent ACC/AHA statement.(9)

QT prolongation without torsade

There remains considerable variation in practice in the management of patients with clinically important QT prolongation (e.g. above the nomogram at-risk line) in the absence of observed episodes of TdP. If feasible, the predicating drug should be discontinued and other modifiable risk factors addressed, including correction of oxygen saturation and plasma potassium, calcium and magnesium, concentrations as necessary. Potassium administration to achieve a concentration between 4.7 and 5.2 mmol/L has been shown to shorten QT interval and reduce QT dispersion in human volunteers administered quinidine.(21)

Patients with clinically important QT prolongation should undergo continuous ECG monitoring; the QT interval on the 12 lead ECG should be re-evaluated periodically, with the frequency depending on the clinical circumstances and the extent of QT prolongation.

Some clinicians administer intravenous magnesium sulphate to patients with QT prolongation in the absence of TdP,(3) but this is probably unnecessary unless multiple risk factors are present and especially if ECG features suggest instability, such as frequent premature contractions or unstable T/U intervals. Although risks from magnesium administration are small, the risk of harm from TdP is also low in appropriately monitored hospitalised patients with isolated aLQTS and there is currently no evidence of benefit. Because magnesium does not affect the QT interval, it is not possible to measure response.

Torsades de pointes

Prolonged episodes of continuous TdP associated with severe hypotension or cardiac arrest should be terminated by electrical cardioversion.(9) It is more typical, however, for TdP to occur in recurrent self-terminating bursts. Under these circumstances treatment is directed at stabilising the myocardium using magnesium sulphate and by shortening repolarisation by increasing heart rate using chronotropic drugs such as isoproterenol (isoprenaline) or cardiac pacing.(20) Benefit may also be obtained using antiarrhythmic drugs, although some of these, especially class 1a and class 3 agents, may worsen the arrhythmia.

As for isolated QT prolongation, responsible agent(s) should be discontinued and modifiable risk factors such as hypokalaemia, hypomagnesaemia and hypoxia should be addressed. Several sources recommend that serum potassium is maintained in the high normal range (4.5-5.0 mmol/L), although evidence is limited.(9, 20)

Magnesium sulphate

Administration of magnesium sulphate is currently recommended as immediate first line treatment for torsades de pointes.(20) The mechanism for benefit is uncertain,(9) but magnesium may reduce the amplitude of EADs by inhibiting the late calcium influx via L-type calcium channels that is associated with delayed ventricular repolarisation. As a result, EADs are less likely to reach threshold potential and provoke or sustain TdP.(22) As a co-

factor for the sodium potassium ATPase, magnesium may stabilise the membrane potential by facilitating potassium influx, correcting dispersed repolarisation without shortening the action potential duration. Efficacy has not been demonstrated in a randomised controlled trial, but in a case series of 12 adult patients with TdP (in 9 induced by antiarrhythmic drugs) a single 2g (8 mmol) dose of magnesium sulphate administered intravenously over 1-2 minutes caused resolution in 9 patients, with a second dose being effective in the remaining 3, without reducing the QT interval.(23) Similar results were reported from a French study, where TdP was completely abolished after administration of intravenous magnesium 1-3 g in 4 of 6 patients. In the remaining 2 patients, TdP improved but recurred in one and was suppressed only partially in the other.(24) An initial intravenous bolus of 2.3-12 mg/kg magnesium sulphate gave a complete response in 5 of 6 children with congenital or acquired LQTS, including both of the children with acquired LQTS. The serum magnesium concentration was 3.9 +/- 1.0 mg/dL (1.60 +/- 0.4 mmol/L) with a range of 2.9-5.4 mg/dL (1.2-2.2 mmol/L) immediately after bolus injection. (25)

Magnesium therapy is simple and relatively safe to administer. Recommended doses in the UK are shown in Table 3. The most prominent adverse effect is flushing, but nausea and vomiting, hypotension, and drowsiness can occur, especially with higher doses. Substantial hypermagnesaemia may cause confusion, slurred speech, double vision, neuromuscular blockade, respiratory depression, hypophosphatemia, hyperosmolar dehydration, cardiac arrhythmias, coma and cardiac arrest. Severe toxicity is usually encountered with concentrations >3.5 mmol/L.

Isoproterenol

Isoproterenol (isoprenaline) increases the heart rate due to non-selective beta1/beta2 adrenoceptor agonist actions; this shortens the QT interval and effective refractory period. In a dog model, isoproterenol prevented quinine-induced TdP. (26, 27) There are no randomised controlled trials of isoproterenol use for TdP in humans, but occasional case

reports suggest benefit.(28) It is probably particularly useful as a bridge to temporary pacing in patients unresponsive to magnesium sulphate. Dose recommendations are shown in Table 3. Isoproterenol may, however, be contraindicated in congenital LQTS as it may prolong QT interval and induce early afterdepolarisations (29) and may also enhance dispersion of repolarisation in some subtypes.(30) It may also worsen ventricular tachycardia if this is not TdP. Other adverse effects include palpitations and flushes and worsening of cardiac ischaemia or hypertension.

Atropine is an alternative pharmacological method for increasing heart rate. It not only increases heart rate but also supresses QT prolongation and TdP induced by intracoronary acetyl choline in patients with cLQTS. (31) Although atropine has been used to for treatment of TdP,(32) it is not usually recommended as it can induce paradoxical bradycardia with consequent worsening of the arrhythmia.(33)

Pacing

Transvenous pacing increases the heart rate, prevents pauses and can suppress or abolish episodes of TdP. Animal models indicate efficacy for pacing in dofetilide-induced torsade,(34) although in a dog model atrial pacing was relatively ineffective at preventing quinidine-induced torsade.(27) Case reports and case series in humans have suggested benefits from pacing for treating TdP induced by quinidine, disopyramide,(35) sotalol (36) or amitriptyline(37), including in patients unresponsive to magnesium sulphate.(38) Evidence suggests that pacing rates of at least 70/min are required; (39) typically rates of 100 to 110 /min are used, while occasionally rates of up to 140 / min may be needed. (38, 40) Pacing is generally considered as an option after magnesium sulphate. Its efficacy in comparison to isoproterenol is uncertain, but it may be a better option when the risk of torsade may persist over longer periods, for example with longer acting precipitant drugs.

Antiarrhythmic drugs

Few patients experiencing TdP fail to respond to the steps described above, and use of conventional antiarrhythmic drugs is rarely required. Those that prolong repolarisation, the class 1a or III drugs, may in theory worsen TdP and should be avoided. There is, however, limited evidence of benefit from use of class 1b agents. Lidocaine was effective in dog (27) and rabbit (41) models of TdP and there are case reports of benefit for treating TdP in humans.(42, 43) Phenytoin has also been reported to be successful in case reports.(28, 44)

Novel approaches

Several drugs are in development to enhance delayed rectifier conductance and these may have future value for treatment of aLQTS. One of these, NS1643, supressed dofetilide-induced QT prolongation and TdP in a rabbit model.(45) Activators of cardiac ATP-sensitive potassium channels (K_{ATP}) such as pinacidil and cromakalim have also had beneficial effects for aLQTS associated with some but not all culprit drugs.(46)

Alpha-2 adrenoceptor agonists attenuate L-type calcium channels and supress EADs. Promising results were obtained for clonidine and dexmedetomidine, with both drugs shortening the QT interval and reducing the incidence of TdP in a rabbit model of aLQTS. (47)

The anti-ischaemic agent ranolazine blocks the late sodium current which is responsible for prolonging action potential duration and which also makes a contribution to EADs and has been shown to prevent or terminate clofilium-induced TdP in rabbits. It may, however, prolong action potential duration and QT interval at higher concentrations due to Ikr blockade. (41)

EADs are facilitated by protein kinases and there is limited evidence that kinase inhibition may be a viable antiarrhythmic strategy, reducing inducibility of TdP.(48)

Aftercare

In patients with aLQTS, the risk of further episodes of TdP is substantially reduced once precipitants and/or culprit agent have been removed and this should result in normalisation of the QTc interval. If it does not, further evaluation to exclude cLQTS should be considered, including obtaining a family history focusing on syncope, epilepsy and/or sudden death. Cardiological and genetic evaluation will then be required for patients to confirm evidence for the condition and for the family members of those in whom cLQTS is confirmed.(49)

In view of the widespread use of QT prolonging drugs, it is important that these are not prescribed inadvertently to patients who have previously experienced TdP, as the risk of further episodes would be high. (50) Patients and their primary clinicians should be alerted to this risk and to available sources of information about these drugs.(18)

Competing interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

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TABLE 1. Examples of currently marketed drugs that have been associated with torsade de pointes

Antiarrhythmics		***Antipsychotics***	Haloperidol
Class Ia	Quinidine		Pimozide
	Disopyramide		Thioridazine
Class Ic	Flecainide		Chlorpromazine
Class III	Amiodarone		Amisulpride
	Dofetilide		
	Dronedarone		
	Ibutilide		
	Sotalol		
Anaesthetics	Sevoflurane	***Antidepressants***	Citalopram
	Propofol		Escitalopram
			Amitriptyline
Antimalarials	Chloroquine	***Anticancer***	Arsenic trioxide
	Halofantrine		Vandetanib
			Sunitinib
Antimicrobials		***Others***	Cocaine
			Methadone
Macrolides	Azithromycin		Ondansetron
	Clarithromycin		Domperidone
	Erythromycin		Anagrelide
Quinolones	Levofloxacin		Donepezil
	Moxifloxacin		Cilostazol
Others	Pentamidine		
	Fluconazole		
	Ketoconazole		
	HIV		

TABLE 2. Examples of potential pharmacokinetic interactions affecting drugs that prolong the QT interval, inhibit cytochrome P450 (CYP) inhibitors, or both.

	CYP isoform affected		
	CYP1A2	**CYP2D6**	**CYP3A4**
QT prolonging drugs	Haloperidol Amitriptyline Imipramine	Amitriptyline Haloperidol Imipramine Quinidine	Erythromycin SSRIs† Amiodarone Cisapride Haloperidol Quinidine Pimozide Methadone
CYP inhibitors	Flouroquinolones* Cimetidine Amiodarone* Grapefruit juice	Ritonavir SSRIs* Amiodarone* Quinidine* Methadone*	Protease inhibitors Imidazole fungicides* Diltiazem SSRIs†* Erythromycin* Grapefruit juice

*May also prolong QT interval

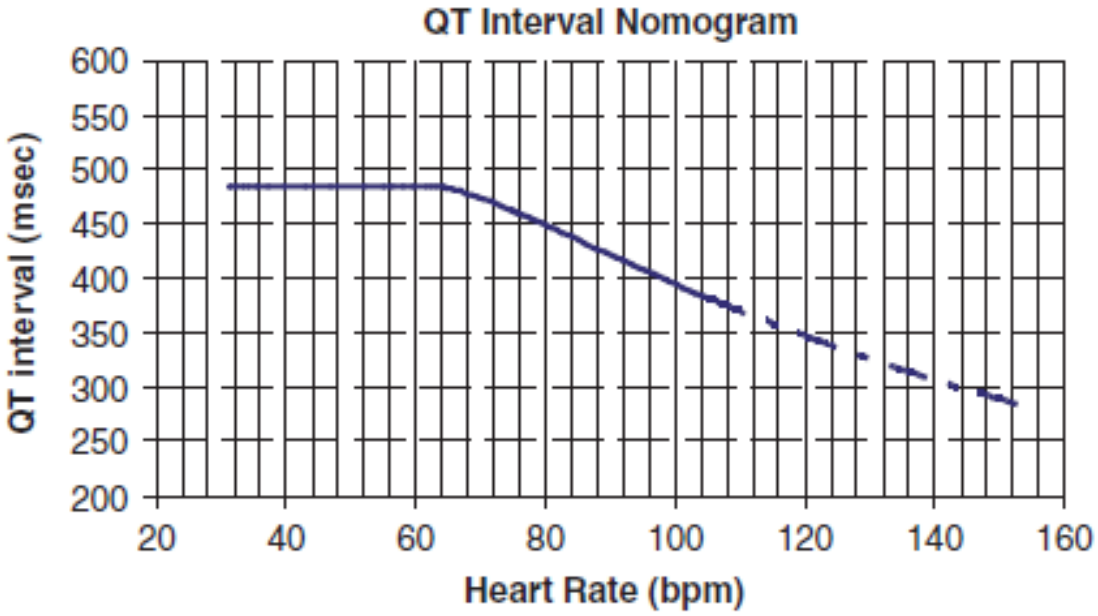
†Selective serotonin reuptake inhibitors

TABLE 3. Drugs used for treating torsades

	Dose (adult)	Notes
Magnesium sulphate	Adults - 2 g* (8 mmol) Children - 25-50 mg/kg* (0.1-0.2 mmol/kg) to maximum of 2 g.	Give as IV infusion over 10-15 minutes Measure plasma magnesium after administration Repeated doses may be needed
Isoproterenol	Adults - 0.5-5 mcg/min Children – 0.1-1.0 mcg/kg/min	Give as continuous IV infusion An initial bolus of 20-60 mcg may be used in adults (0.3-1 mcg/kg in children) Titrate infusion rate to heart rate of 90-110. Higher heart rates may be used if torsades recurs.

*Magnesium sulphate heptahydrate

Figure 1. QT interval nomogram for determining ‘at risk’ QT-Heart rate pairs from a single 12-lead ECG. Reproduced from reference (11), with permission.


QT Interval Nomogram
QT interval (msec)
600
550
500
450
400
350
300
250
200
20
40
60
80
100
120
140
160
Heart Rate (bpm)