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REVIEW

Cellular basis of drug-induced torsades de pointes

DM Roden[1,2]

[1]*Department of Medicine, Vanderbilt University School of Medicine, Nashville, TN, USA and* [2]*Department of Pharmacology, Vanderbilt University School of Medicine, Nashville, TN, USA*

Striking QT prolongation and the morphologically distinctive ventricular tachycardia torsades de pointes can occur in up to 5% of patients treated with certain antiarrhythmic drugs. This adverse drug reaction also occurs, albeit far less frequently, during therapy with a range of drugs not used for cardiovascular indications; examples include certain antibiotics, antipsychotics and antihistamines. The common mechanism for drug-induced torsades de pointes is inhibition of a specific repolarizing potassium current, I_{Kr}. The key question facing clinicians, regulators and those who develop drugs is why torsades de pointes only occurs in some patients exposed to I_{Kr} block. This paper reviews the clinical, cellular, molecular and genetic features of the arrhythmia that may provide an answer to this question and proposes future studies in this area.
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Abbreviation: EAD, early afterdepolarization

Introduction

Shortly after the antiarrhythmic quinidine was introduced into practice in the 1920s, the phenomenon of 'quinidine syncope', sudden loss of consciousness usually with initiation of therapy, was described. The mechanism, however, remained obscure until 1964 when Selzer and Wray (1964) reported a distinctive form of polymorphic ventricular tachycardia causing quinidine syncope. The term 'torsades de pointes' was coined by Dessertenne (1966), when he described a morphologically distinctive polymorphic ventricular tachycardia occurring in an elderly woman with high-grade atrial ventricular block and current syncope. The term has been translated as 'twisting of the points' referring to the slowly changing QRS axis during a prolonged episode of tachycardia.

Interestingly, although both of these early reports noted the polymorphic tachycardia, neither commented on what is now recognized as the second critical feature of the torsades de pointes syndrome, marked prolongation and deformity of the QT interval. Indeed, although the term torsades de pointes has been used to describe virtually any polymorphic ventricular tachycardia, it is now apparent that there is a mechanistic link between QT prolongation and subsequent development of the arrhythmia. Therefore, most authorities suggest that the term torsades de pointes be confined to describe those polymorphic tachycardias that occur in the setting of marked QT prolongation. This is especially important as therapies commonly used for torsades de pointes, such as catecholamine infusion, may be detrimental in other forms of polymorphic tachycardia. In this review, the use of the term 'torsades de pointes' is confined to those tachycardias with markedly prolonged QT intervals.

Correspondence: Dr DM Roden, Departments of Medicine and Pharmacology, Vanderbilt University School of Medicine, 1285 Medical Research Building IV, Nashville, TN 37232, USA.
E-mail: dan.roden@vanderbilt.edu
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Causes of torsades de pointes

Drug administration is the commonest cause of torsades de pointes. The most frequent offenders are QT-prolonging antiarrhythmics, such as quinidine, sotalol, dofetilide or ibutilide; with these agents, 1–8% of patients develop marked QT prolongation and torsades de pointes (Lown and Wolf, 1971; Soyka *et al*., 1990; Torp-Pedersen *et al*., 1999; Kober *et al*., 2000). On the other hand, the torsades de pointes syndrome is now well recognized with a wide range of drugs developed for non-cardiovascular indications. These include high-profile drug withdrawal cases, such as terfenadine, astemizole and cisapride, as well as a variety of drugs that are in common clinical use, such as methadone, erythromycin and other antibiotics, and thioridazine and other antipsychotics; an up-to-date list is maintained at the www.torsades.org website. The incidence of torsades de pointes with these 'non-cardiovascular' agents is very much lower than with QT-prolonging antiarrhythmics. Nevertheless, the development of a serious adverse effect such as

torsades de pointes can upset the real or perceived balance between risk and benefit that underlies any decision to approve a drug (by regulators) or to prescribe a drug (by practitioners) (Viskin *et al*., 2003; Roden, 2004).

Other causes of torsades de pointes include bradycardia (as in Dessertenne's index case), hypokalaemia and the congenital long QT syndromes, whose relationship with the drug-induced form is discussed further below; these other causes for torsades are also risk factors for the drug-induced arrhythmia. In addition, certain forms of heart disease are also increasingly well recognized as risk factors for drug-induced torsades de pointes; these include congestive heart failure, left ventricular hypertrophy and the hours following conversion of atrial fibrillation to sinus rhythm (Choy *et al*., 1999). Historically, a first clue to the propensity of a drug to produce torsades de pointes was the recognition of the arrhythmia during accidental or intentional overdose. This was the case with sotalol and terfenadine, and in general, the risk of torsades de pointes increases monotonically with plasma drug concentration (Neuvonen *et al*., 1981; Davies *et al*., 1989). The risk for torsades de pointes due to drug accumulation is greatest for agents that undergo elimination by a single pathway, such as hepatic metabolism by one cytochrome or by renal excretion. In such cases, inhibition of the elimination pathway can result in marked accumulation of the parent drug and an increased risk for dose-related toxicity, including torsades de pointes. Most reported cases of torsades de pointes with cisapride or terfenadine were due to either overdose or inhibition of CYP3A, the major elimination pathway for these agents (Woosley *et al*., 1993; Barbey *et al*., 2002). Similarly, the risk of torsades de pointes is increased when usual doses of sotalol or dofetilide are used in patients with renal dysfunction, as renal elimination is the major route of elimination for these drugs (Mounsey and DiMarco, 2000; Reiffel and Appel, 2001). An exception is quinidine, where torsades de pointes tends to occur at low (even 'subtherapeutic') concentrations (Koster and Wellens, 1976; Roden *et al*., 1986). One possible explanation is that the risk of torsades is mediated by accumulation of an active metabolite, but clinical and *in vitro* studies argue against this possibility (Thompson *et al*., 1987, 1988). The most likely explanation is that at low concentrations, quinidine prolongs QT interval (through mechanisms discussed below), but at higher concentrations, the drug exerts other electrophysiologic actions (notably sodium channel block) that in turn limit QT prolongation (Antzelevitch *et al*., 1999).

Ascertaining drug-induced torsades de pointes

Ascertainment of cases of torsades de pointes presents its own special set of issues. Even a typical case, with classical electrocardiographic findings, can sometimes be difficult to attribute to a drug. Affected patients may have advanced underlying heart disease, polypharmacy and co-morbid conditions, such as hypokalaemia or bradycardia. In such settings, the recent initiation of a drug, especially at unusually high drug dosages (or attaining unusually high concentrations), is often the major piece of evidence. Given what is known about torsades de pointes from records of patients with the arrhythmia in the hospital, it seems likely that another mode of presentation would be sudden unexpected death. Increased mortality has been seen with QT-prolonging antiarrhythmics (although difficult to attribute definitively to torsades de pointes) (Waldo *et al*., 1996; Pratt *et al*., 1998). More recently, an increase in mortality in patients receiving certain non-cardiovascular drugs has also been reported, and may be attributable to torsades de pointes. For example, in an examination of the Tennessee Medicaid database, Ray *et al*. (2004) found a strikingly increased incidence of sudden death among those using erythromycin and inhibitors of CYP3A, the major pathway for erythromycin elimination. Similarly, pharmacoepidemiologic data have implicated certain antipsychotic drugs, known to produce torsades de pointes in other settings, in increased mortality among some patients receiving these agents (Hennessy *et al*., 2002). It is also possible that such increases in death rates reflect not only torsades de pointes but also other (perhaps even as yet unidentified) mechanisms.

Underlying electrophysiologic mechanisms: cellular level

First principles in cardiac electrophysiology dictate that an increase in QT interval must reflect an increase in action potential duration in at least some regions of the ventricle. Such increased action potential duration, in turn, must reflect an increase in inward current or a decrease in outward current. Indeed, both mechanisms have been described in subforms of the congenital long QT syndrome (Keating and Sanguinetti, 2001). However, the vast majority of drugs associated with torsades de pointes are thought to act by reducing one specific potassium current, the so-called rapid component of the delayed rectifier, I_{Kr} (Haverkamp *et al*., 2000; Fenichel *et al*., 2004). Expression of the human-ether-à-go-go related gene (*hERG*, now termed *KCNH2*) in heterologous systems recapitulates a channel (Kv11.1) with gating and pharmacologic sensitivities similar to human I_{Kr} (Sanguinetti *et al*., 1995). Accordingly, a common first step in screening drugs for potential torsades-related activity is to assess their actions in such heterologous systems (Haverkamp *et al*., 2000; Fenichel *et al*., 2004). As discussed elsewhere in this symposium, there is some uncertainty about which heterologous system and which specific experimental conditions are optimal for this type of experiment. Issues that have not been settled include which, if any, subunits reported to co-express with *KCNH2* to modify I_{Kr} function should be included (Yang *et al*., 1995a; Abbott *et al*., 1999), and the specific voltage clamp conditions to be used. Given such uncertainties, it is mandatory to include positive and negative controls with each experiment.

Although screening drugs for acute I_{Kr} block is becoming standard in the pharmaceutical industry, it is important to recognize the formal possibility that other mechanisms may contribute to drug-induced QT prolongation and the risk of torsades. At least one drug, DPI-201, formerly in development as a positive inotropic agent, is thought to prolong QT

intervals, and cause torsades, by enhancing inward current through sodium channels (Buggisch *et al.*, 1985; Kuhlkamp *et al.*, 2003). A similar enhancement of inward current (through sodium or calcium channels) has also been suggested as a mechanism for QT prolongation by ibutilide (Lee and Lee, 1998), which also blocks I_{Kr} (Yang *et al.*, 1995b). As outlined elsewhere in this symposium, there is a newer recognition that drugs may also reduce *KCNH2*-mediated current not by channel block, but rather by reducing cell surface expression of functional channels, likely by reducing trafficking of mature channels to the cell surface. This mechanism has been reported for arsenic (Ficker *et al.*, 2004) and pentamidine (Kuryshev *et al.*, 2005), and both compounds are well recognized as causes of torsades de pointes. Thus, a drug that does not acutely block I_{Kr} in heterologous expression systems may still be associated with QT prolongation during clinical therapy. However, the mechanisms to identify such compounds have not yet been worked out well and the number of compounds that produce torsades de pointes through non-I_{Kr} block-mediated mechanisms is not yet established.

Structure–function studies have identified features of the *KCNH2* channel pore that appear important for drug block (Mitcheson *et al.*, 2000a). One of these is lack of two key proline residues in the S6 region; the lack of these residues probably underlies the unusually 'wide' mouth of the channel that can thereby accommodate and trap (Mitcheson *et al.*, 2000b) relatively bulky drugs that cannot access the intracellular pore for other potassium channels. The second key feature is the presence of multiple aromatic residues within the channel pore that are thought to serve as high affinity binding sites for many drugs of diverse structures. Modelling the interactions of a drug series with the channel using this information is complementary strategy to predict high potency I_{Kr} blockers (Aptula and Cronin, 2004; Aronov, 2005; Tobita *et al.*, 2005).

Underlying electrophysiologic mechanisms: multicellular level

Exposure of cells from the canine conduction system (Purkinje fibres) to conditions mimicking human torsades de pointes (action potential prolonging drugs, hypokalaemia, slow drive rates) produces action potential prolongation followed by a distinctive morphologic change in the trajectory of terminal repolarization (termed an early afterdepolarization, or EAD) and eventually, triggered upstrokes arising from the EAD (Roden and Hoffman, 1985). The initial action potential prolongation reflects block of I_{Kr} (or of other potassium currents or even enhanced inward current, depending upon the experimental condition). However, the development of the EAD and the triggered activity reflect enhanced inward current through additional arrhythmogenic mechanisms; most experiments suggest that these late arrhythmogenic currents are carried through either L-type calcium channels or the sodium–calcium exchanger (Nattel and Quantz, 1988; Szabo *et al.*, 1994). Further, abnormalities of intracellular calcium handling, such as those seen in heart failure, can enhance such arrhythmogenic inward current (Wu *et al.*, 1999) and may account for increased risk of torsades in patients with contractile dysfunction.

These data implicate triggered beats arising from EADs in the conduction system as a candidate initiator for torsades de pointes. Studies in the left ventricular 'wedge' preparation, which includes all layers of the myocardium, have added an important dimension to our understanding of torsades de pointes and indeed of other unstable reentrant arrhythmias (Yan *et al.*, 1998; Antzelevitch *et al.*, 1999). A key finding in the wedge preparation is transmural heterogeneity of action potential duration, with the longest action potentials in the mid-myocardium (the 'M-cell' layer) and subendocardial Purkinje fibres, and shorter action potential durations in the epicardium and endocardium. Such physiologic action potential heterogeneity is exaggerated under experimental conditions producing torsades de pointes (drug + slow drive rate + hypokalaemia) and indeed spontaneous unstable reentrant rhythms resembling torsades de pointes have been recorded in wedge preparations under these conditions (Antzelevitch *et al.*, 1996). Whether the initiator is a triggered beat from an EAD in the Purkinje network or some other mechanism remains uncertain. In preparations that do not display spontaneous arrhythmias, stimulation from regions of very short action potentials (generally epicardium) can also provoke apparent reentrant excitation. Thus, the wedge preparation has identified physiologic heterogeneity of action potential durations that is exaggerated under pathological conditions to create a substrate that is vulnerable to unstable reentrant excitation. This mechanism has now been suggested for other types of unstable reentrant, such as those seen Brugada syndrome or the more recently recognized short QT syndrome (Yan and Antzelevitch, 1999; Extramiana and Antzelevitch, 2004). Whether drugs can provoke increased heterogeneity of transmural repolarization without altering the duration of the surface QT interval is not certain. Should such drugs exist, they could be associated with polymorphic ventricular tachycardias that would be faster (and thus even more unstable) than typical torsades de pointes. In this case, the 'signal' that such a drug would generate might simply be an increase in mortality, in all or even a subset of exposed patients. Such a safety signal would be quite difficult to identify, but the science underlying torsades de pointes does raise this possibility.

Mechanisms underlying variability in the risk of torsades

The 'chain of evidence' from drug block of *KCNH2* channels to action potential prolongation to heterogeneity of repolarization to unstable reentry underlies the development of clinical torsades de pointes (Roden and Viswanathan, 2005). However, it is very clear that even among high-risk patients exposed to high-risk drugs, not all will develop the arrhythmia. Indeed, even among patients with the most grotesque QT prolongation due to the congenital long QT syndrome, the vast majority of heart beats are not, in fact, followed by torsades de pointes. Thus, there must be

modulatory activities at some, if not all, links in this chain that reduce the risk of torsades from 100% to some smaller number, often a very much smaller number. One modulator is plasma drug concentration, mentioned above. In addition, it is formally possible that intracellular drug concentrations are actually highly variable because of variable drug transport into or out of myocardial cells; this possibility is only now beginning to be tested (McBride *et al.*, 2005; Grube *et al.*, 2006).

Cardiac repolarization is not determined solely by I_{Kr}, but rather reflects a complex interplay among this current, other repolarizing currents (such as I_{TO}, I_{Ks} and I_{K1}), and inward currents through calcium or sodium channels or through mechanisms such as sodium–calcium exchange. This complex biology is further regulated by the external environment, notably extracellular potassium, heart rate and adrenergic tone. Thus, the development of torsades de pointes likely reflects both a vulnerable substrate as well as arrhythmogenic triggers that further modify the repolarization process and its heterogeneity.

Repolarization reserve and genetic predisposition to drug-induced torsades

Although I_{Kr} is increasingly recognized as a major repolarizing mechanism in human heart, there is some redundancy in this system. Recent studies suggest that a major role for the slow component of the delayed rectifier, I_{Ks}, is to guard against excess action potential prolongation when I_{Kr} is reduced (Jost *et al.*, 2005; Roden and Yang, 2005; Silva and Rudy, 2005). I_{Ks} is generated not by expression of *KCNH2*, but of two different genes, *KCNQ1* (formerly known as *KvLQT1*) encoding the pore-forming α-subunit and *KCNE1* (formerly known as minK), encoding an important function-modifying ancillary β-subunit. Mutations in *KCNQ1* are the commonest form of the congenital long QT syndrome and epidemiologic data indicate that most *KCNQ1* mutation carriers do not, in fact, develop any symptoms over a lifetime (Priori *et al.*, 2003). We have termed this situation 'reduced repolarization reserve': we hypothesize that repolarization is a physiologically redundant process so that I_{Kr} block will not result in markedly prolonged repolarization, that is, the system displays some 'reserve' (Roden, 1998, 2006). However, otherwise subclinical lesions in other components of the repolarization system, such as the reduction of I_{Ks} (Donger *et al.*, 1997; Napolitano *et al.*, 2000; Yang *et al.*, 2002) or enhanced I_{Na} (Makita *et al.*, 2002) due to genetic factors, may become apparent as marked QT prolongation when I_{Kr} is reduced. Thus, a major effort is currently being devoted to the question of whether genetic variants that are asymptomatic and subclinical at baseline may nevertheless increase the risk for torsades de pointes upon drug exposure. The genes encoding I_{Ks} represent one very attractive set of candidates for such susceptibility and indeed cases of drug-induced torsades de pointes have now been reported in patients with previously subclinical congenital long QT syndrome (Donger *et al.*, 1997; Napolitano *et al.*, 2000; Yang *et al.*, 2002). Other genes encoding ion currents important for repolarization, such as calcium channels or sodium channels, are by the same logic equally attractive candidates. The list of candidate genes and pathways in which variable expression or function (due to DNA variants and/or disease) can modulate the risk of torsades thus can include those encoding other ion channels, important exchangers, mechanisms controlling intercellular calcium release and reuptake from the sarcoplasmic reticulum, important anchoring proteins, adrenergic control systems and the protein complexes that link cells to each other, to name but a few. Studies of this hypothesis are in their infancy, but have already implicated a common polymorphism in the coding region of the cardiac sodium channel (Splawski *et al.*, 2002) and a variant haplotype in a non-coding region of *KCNQ1* (Kaab *et al.*, 2005) as potential risk factors for drug-induced torsades de pointes. The execution of further studies in this area requires collaborations to generate very large sets of well-phenotyped patients, and sophisticated techniques in high-throughput genotyping and genetic epidemiologic analysis of the results of such genotyping.

Conclusion

Although drug-induced torsades de pointes has been recognized for 40 years, it is only in the last decade and half that it has moved from an electrophysiologic curiosity to an important component of the drug development process. This change has been driven by diverse factors, including advances in molecular genetics (allowing identification of various forms of the congenital long QT syndrome, including subclinical ones), recognition of torsades de pointes as an unusual arrhythmia often linked to initiation of drug therapy and the increasing characterization of individual molecular pathways, such as CYP3A, for drug elimination.

Although the problem has been increasingly well recognized, such recognition carries with it further problems. A major issue in the field at this point is that although many drugs reduce I_{Kr}, the risk of torsades associated with an I_{Kr}-blocking drug in an individual patient, or in hundreds of thousands of exposed patients, has been very much more difficult to estimate. Thus, paradoxically, an increase in our molecular understanding of this relatively rare adverse drug effect has had two important consequences. First, it is very unlikely that any drug causing torsades de pointes through mechanisms similar to those with terfenadine or cisapride will ever reach the market again. These drugs are very high potency I_{Kr} blockers, and screening methodologies are in place to identify such compounds before imposing a large cost burden on the development process. Conversely, however, the imperfections in the chain of events leading from I_{Kr} block to full-blown torsades remain very poorly understood. This in turn has generated the second important consequence of new knowledge in this area, namely a slowing of the drug development process because of uncertainties of the way in which very early preclinical markers such as I_{Kr} block can translate into risk that can then be balanced against potential benefits of new therapies.

This is not a problem unique to I_{Kr} block. Studies in this area highlight the way in which drugs can have unanticipated consequences because they act within a very

complicated biologic context, such as disease-associated cardiac repolarization (Roden, 2005). It seems likely that other rare but potentially important adverse drug effects may similarly reflect drug interactions with a complex biologic substrate. Thus, an important goal for this symposium has been to further define experimental approaches that may be useful in refining our understanding of the mechanisms underlying the arrhythmia, and hence, our ability to predict in an individual or in a population. Such a systems approach may extend to other areas of drug development and risk–benefit assessment.

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Conflict of interest

Dr DM Roden has received consulting fees from Avanir, Baker Brothers Advisors LLC, Cardiokine Inc., Eli Lilly, Astra Zeneca, Adolor, Cardiome and CardioDx. He receives reimbursement from Novartis as a member of the Data Safety and Monitoring Board. He reports holding a patent on D85N as a predictive SNP for drug-induced long QT syndrome.

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