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Clinical aspects of ventricular arrhythmias associated with QT prolongation

W. Haverkamp, L. Eckardt, G. Mönnig, E. Schulze-Bahr, H. Wedekind, P. Kirchhof, F. Haverkamp and G. Breithardt

Department of Cardiology and Angiology, Hospital of the University of Münster, and Institute for Arteriosclerosis Research at the University of Münster, Germany

QT interval prolongation is a risk factor in a number of cardiovascular as well as non-cardiovascular diseases. Apart from this, abnormal, i.e. excessive, QT prolongation is typical for patients with acquired as well as congenital long QT syndrome. In these syndromes, prolongation of repolarization is often associated with severe, potentially life-threatening, ventricular tachyarrhythmias of the type torsade de pointes (TdP). While the congenital long QT syndrome has recently been identified as an ion channelopathy, the mechanisms underlying acquired long QT syndrome, which is most often induced by drugs prolonging myocardial repolarization, are far from understood. Recent studies have yielded only a small number of individual cases in whom the clinical setting has suggested an acquired form of the syndrome and genetic analysis revealed a familial form.

In order to prevent an unwanted exposure to risk, physicians prescribing agents that may prolong repolarization need to be aware of their potential to cause excessive QT prolongation and TdP. A clearer delineation of the factors predisposing to abnormal prolongation of repolarization and TdP, and a more precise quantification of the torsadogenic potency of individual drugs appear mandatory in order to prevent, or at least minimize, the incidence of this potentially fatal adverse effect of certain drugs.
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Key Words: Long QT syndrome, torsade de pointes, QT interval, proarrhythmia, ventricular tachycardia, sudden cardiac death, drug metabolism, adverse effect.

Prognostic significance of QT interval prolongation

The QT interval reflects the time between the initial fast depolarization of the ventricle and its subsequent repolarization. Since the duration of depolarization is strongly dependent on heart rate, QT intervals need to be corrected for heart rate. The Bazett equation has been most frequently for heart rate correction, although several limitations of the equation are obvious. A prolonged heart rate corrected QT interval (QTc) on the 12-lead electrocardiogram may be associated with an increased risk for ventricular arrhythmias and sudden death which has been reported in, e.g. patients after mycardial infarction, with cardiomyopathy, and in diabetic patients with autonomic neuropathy. The exact mechanisms underlying the association between prolongation of QTc and an increased mortality risk in these patients are still unclear. Disturbances of autonomic cardiac innervation, left ventricular hypertrophy, ischaemia and overweight, besides others, seem to play a role. However, in these patient groups the extent of QT prolongation is usually small, QTc most often does not exceed values of 450–460 ms. As the same values have been considered 'borderline', it is not surprising that the positive predictive value of prolongation of the QT interval is relatively low.

However, under certain circumstances, the extent of QT prolongation is much more pronounced, e.g. in patients with acquired and congenital long QT syndrome[1–4]. In these patients, the QTc value may exceed 600 ms. In this situation, life-threatening ventricular tachyarrhythmias of the torsade de pointes (TdP) type are likely to occur. It is important to note that the above form of QT prolongation, that may be present in various types of cardiac and non-cardiac diseases, and acquired as well as congenital QT prolongation are two distinct forms of prolongation of myocardial repolarization. Abnormal, i.e. excessive prolongation, of the QT interval is usually not seen in the former group but is typical for the latter one. It is difficult to establish the threshold for excessive

Correspondence: Dr Wilhelm Haverkamp, Medizinische Klinik und Poliklinik, Innere Medizin C (Kardiologie, Angiologie), Universitätsklinikum Münster, D-48129 Münster, Germany.

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Table 1 Genetic characterization of congenital long QT syndrome

LQT	Locus	Gene	Gene product
LQT1	11p15·5	KCNQ1	α-Subunit of potassium channel (I_{Ks})
LQT2	7q35–36	HERG	α-Subunit of potassium channel (I_{Kr})
LQT3	3p21–24	SCN5A	α-Subunit of sodium channel (I_{Na})
LQT4	4q25–27	Unknown	Unknown
LQT5	21q22·1–22	KCNE1	β-Subunit of potassium channel (I_{Ks})
LQT6	21q22·1–22	KCNE2	β-Subunit of potassium channel (I_{Kr})
LQT7	—	—	—
JNL1	11p15·5	KCNQ1	α-Subunit of potassium channel (I_{Ks})
JNL2	21q22·1–22	KCNE1	β-Subunit of potassium channel (I_{Ks})
JNL3	—	—	—

LQT=Long QT syndrome; JNL=Jervell and Lange–Nielsen syndrome; K_{Kr}=rapidly activating component of the delayed rectifier potassium current I_K; I_{Ks}=slowly activating component of the delayed rectifier potassium current I_K; I_{Na}=rapid sodium inward current.

prolongation of the QT interval. Most authors have considered a QTc value exceeding 0·5 or 0·55 s as abnormally prolonged.

Congenital and acquired long QT syndrome

The congenital form of the long QT syndrome has recently been identified as an ion channelopathy. Mutations causing the disease have been identified in five genes (LQT1–LQT3, LQT5, LQT6), each encoding a cardiac ion channel protein (Table 1)[1,2]. The SCN5A mutations (LQT3) result in defective sodium channel inactivation, whereas KCNQ1 (LQT1), KCNE1 (LQT5), KCNE2 (LQT6), and HERG mutations (LQT2) result in decreased outward potassium current. Either mutation decreases net outward current during repolarization and, thereby, accounts for abnormally prolonged QT intervals on the surface electrocardiogram. So far, the mutant gene for LQT4 which has been mapped to chromosome 4 (4q25–27), has not been discovered.

Acquired abnormal QT prolongation and TdP have been described under a variety of circumstances (Table 2)[3,4]. The most common cause of the arrhythmia seems to be the administration of antiarrhythmic drugs that prolong the action potential, i.e. class IA and class III antiarrhythmic agents. The incidence of TdP in patients treated with quinidine has been estimated to range between 2·0 and 8·8%[5–8]. TdP has also been described to occur during therapy with disopyramide and procainamide both of which have effects on repolarization similar to quinidine. The incidence of TdP associated with sotalol, which besides its class III activity possesses significant beta-blocking activity, has been estimated to range between 1·8% and 4·8%[9–11]. In a series of 396 patients who underwent serial drug testing because of either sustained ventricular tachyarrhythmias or aborted sudden death at our institution, the incidence of TdP was 1·8% (seven patients)[9]. TdP secondary to exposure to newer so-called 'pure' class III agents (e.g. dofetilide, sematalide, d-sotalol, almokalant, ibutilide) and to treatment with N-acetyl-procainamide, the major metabolite of procainamide, has been well documented.

Cases of TdP have not only been reported to occur secondary to treatment with cardiac or antiarrhythmic drugs but also during treatment with several other drugs not generally thought to have significant effects on myocardial repolarization[3,4]. Non-cardiovascular drugs which have been shown to be potentially associated with abnormal QT prolongation and TdP include phenothiazines, antidepressants, other psychotropic drugs, antihistamines of the H1 blocking type, the promotility

Table 2 Causes and conditions leading to acquired QT prolongation and torsade de pointes

Drugs (see Table 4)
Ionic contrast media
Poisoning
Arsenic poisoning
Poisoning with organophosphorus insecticides
Nerve gas
Electrolyte abnormalities
Hypokalaemia
Hypomagnesaemia
Bradyarrhythmias
Sinus bradycardia
AV block
'Relative' bradycardia resulting from frequent ventricular extrasystoles followed by a compensatory pause
Altered nutritional states
Anorexia nervosa
Diets, starvation
Alcoholism
Cerebrovascular diseases
Intracranial and subarachnoideal haemorrhage
Stroke
Intracranial trauma
Hypothyroidism

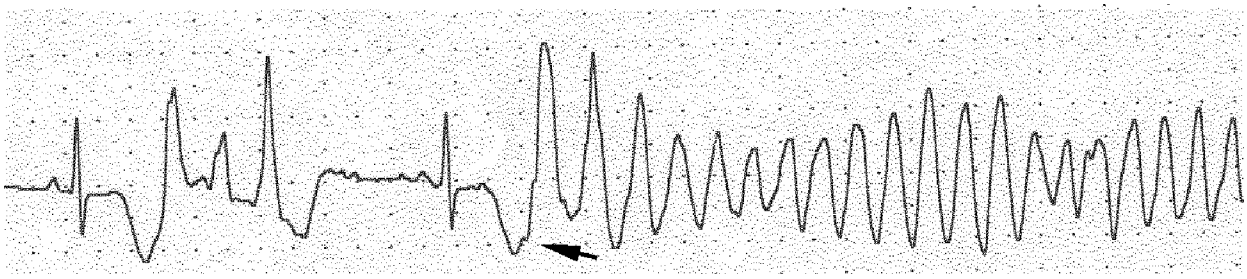

Figure 1 **Monitor strip showing the typical the 'twisting' morphology of TdP. Other polymorphic tachyarrhythmias, however, may also show this morphology. QT interval prolongation, large amplitude T waves (arrow) and a typical onset of the arrhythmia are needed for the diagnosis 'torsade de pointes' (see text for discussion).**

agent cisapride, and some antibiotics, most notably erythromycin. It is noteworthy that these apparently harmless drugs can create life-threatening ventricular arrhythmias, and that physicians can unwittingly expose their patients to risk. Estimation of the incidence of TdP during treatment with non-cardiovascular drugs is difficult. A large number of case reports and individual small series suggest that the occurrence of this particular form of drug-related proarrhythmia is not a trivial problem. All known drugs which may induced TdP share the common property that they block the rapidly activating component of the delayed rectifier potassium current I_{Kr} which plays an important role during the myocardial repolarization process. Although other mechanisms whereby a drug produces prolongation of repolarization may also play a role, the ability of a drug to block I_{Kr} can be considered a prerequisite for the induction of abnormal QT prolongation and TdP[4].

The mechanisms underlying acquired long QT syndrome are far from understood. Currently, we do not know why a drug which prolongs the action potential and exerts antiarrhythmic effects in some patients, may produce excessive QT prolongation and TdP in others. The fact that blockade of I_{Kr} is involved in both the pathogenesis of the congenital as well as the acquired form of long QT syndrome, has led to the suggestion that patients with the acquired form of long QT syndrome may also have gene mutations, e.g. a mutation in the gene encoding for I_{Kr} (HERG). However, recent studies in patients with drug-induced QT prolongation and TdP have yielded only a small number of individual cases in whom the clinical setting had suggested an acquired form of the syndrome and genetic analysis revealed a familial form. In our own series of 17 patients with drug-induced long QT syndrome who underwent SSCP analysis and direct sequencing of the five genes known to cause congenital LQTS, a mutation was found in only four patients (23%)[12]. Similarly, Sesti and coworkers found mutation in the KCNE2 gene in only three out of 98 patients (3%) with drug-induced long QT syndrome. Although these findings do not exclude other channels being involved, they favour a multifactorial origin of acquired LQTS[13]. It is conceivable that modifier genes that influence the pattern and clinical manifestation of the disease and other factors that control the expression and translation of genes may play a role.

Clinical characteristics of TdP

Dessertenne coined the term 'torsade de pointes' to describe the particular feature of the peaks of the QRS complexes ('pointes') which twist around the isoelectric line during the arrhythmia (Figs 1 and 2)[14,15]. Dessertenne selected six consecutive ventricular complexes showing a progressive change in the electrical axis and occurring in 3 s as the lower limit for TdP. However, longer runs of tachycardia usually are necessary to observe the successively changing upward and downward orientation of the QRS complexes. Repeated episodes most often last for 5–20 beats. However, it should be noted that other polymorphic ventricular tachyarrhythmias might have a similar 'twisting' morphology and that the morphology of the arrhythmia alone is not sufficient to make the diagnosis of TdP. Documentation of abnormal QT prolongation and of the onset of the arrhythmia is necessary to correctly identify drug-induced TdP[4]. Drug-induced TdP are typically preceded by a prodromal pause (Fig. 1)[7]. As the long cycle is generally a post-extrasystolic pause, the entire sequence is more completely defined as a 'short–long–short' phenomenon. This pattern can be observed regardless of the drug provoking the arrhythmia. It is also typical for adults with a congenital long QT syndrome. Alterations in T wave morphology, or amplitude and/or abnormal distortions of the T wave are common in both, the acquired as well as the congenital variant of the syndrome (Fig. 1). In addition, U waves distinct from the normal T wave can often been seen. The U waves are usually most visible in the lateral and left precordial leads, while they may be indistinguishable from the T wave in the right precordial leads. When only one lead is available, separation between the T and U components of the TU wave is often difficult. Changes in T wave morphology and the occurrence of U waves constitute important warning signs as they may precede the occurrence of TdP. When U waves are visible in patients with TdP, the arrhythmia usually starts from the peak or the descending portion of the U wave (Fig. 1).

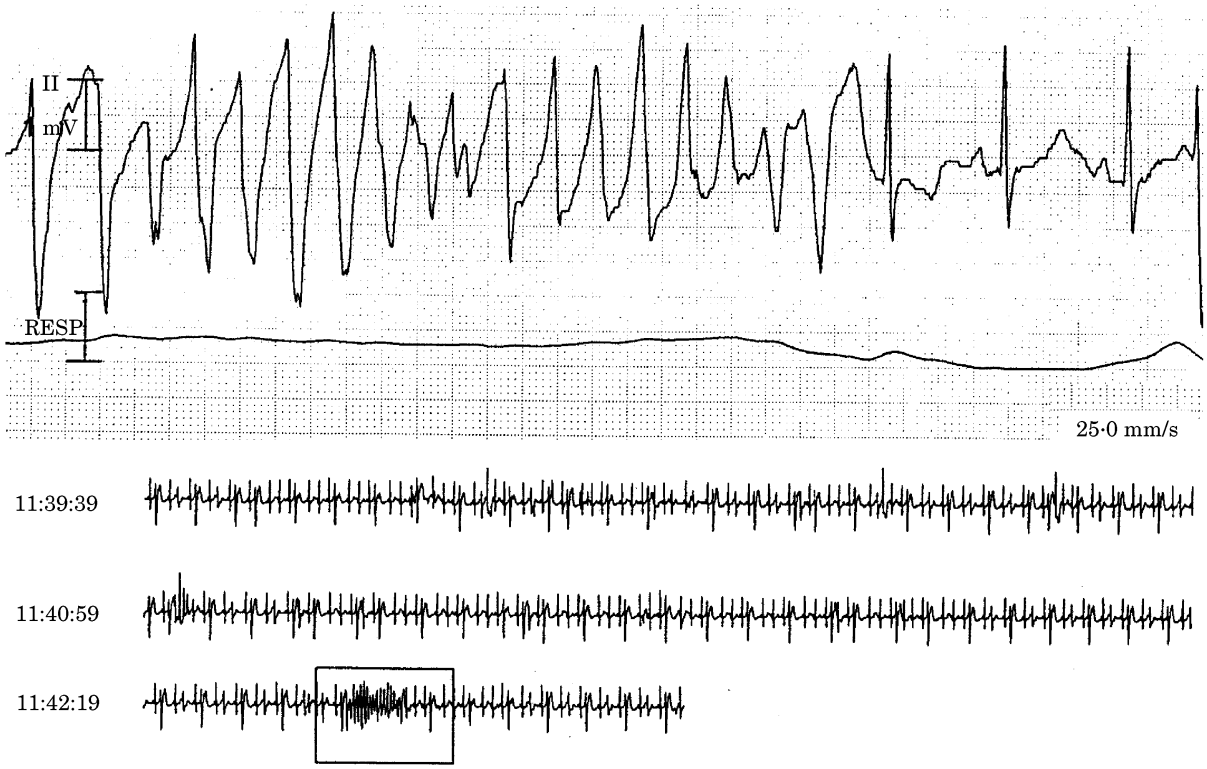

Figure 2 **'Relative bradycardia' resulting from frequent ventricular premature beats followed by a compensatory pause. Finally, a short run of non-sustained TdP occurs.**

The clinical aspects of TdP are heterogeneous. Attacks of TdP may differ in their frequency, duration and severity. In some patients, diagnosis is made by Holter monitoring with the arrhythmia causing no symptoms while in other patients, syncope and, in severe cases, sudden cardia death may result (Fig. 3). Although TdP preferentially occurs shortly after initiation of therapy, it may also develop during long-term treatment. The late occurrence of TdP has been linked to changes in dose, reinitiation of the drug after short discontinuation, new bradycardia, and transient electrolyte disorders such as hypokalaemia and/or hypomagnesaemia. The latter constitute risk factors for the development of drug-related TdP. In general, risk factors outlined in detail in Table 3 play an important in the clinical manifestation of acquired abnormal QT prolongation and TdP.

One important aspect of drug-induced TdP is that patients have been described who developed additional episodes of TdP during subsequent exposure to a repolarization prolonging drug different from the one that initially caused their arrhythmia (Fig. 4). This suggests that drug-induced TdP is not a 'drug-specific response' but a 'patient-specific response'. The latter does not necessarily mean that the individual patient will always show abnormal QT prolongation and TdP during exposure to repolarization prolonging stimuli. This becomes obvious when considering the highly variable intervals between the initiation of drug therapy and occurrence of TdP reported in the literature.

Ion channel blockade and extent of QT prolongation as surrogate parameters for the potency of a drug to produce TdP

Since almost all drugs which may induce TdP share the common property to prolong the QT interval by mostly blockade of I_{Kr}, it is not surprising that both the extent of asymptomatic QT prolongation and extent of I_{Kr} blockade in vitro have become surrogate parameters for the risk of drug-induced TdP[4]. By definition, a surrogate parameter or surrogate end-point is a measurement or a physical sign used as a substitute for a clinically meaningful end-point. In the case of drug-induced proarrhythmia, the end-point is the generation of abnormal, excessive QT prolongation leading to TdP. Changes induced by a therapy on a surrogate end-point (i.e. the extent of QT prolongation and potency of I_{Kr} blockade) are expected to reflect changes in the clinically meaningful end-point (i.e. the frequency of TdP associated with the use of a particular drug). However, there are certain requirements for a surrogate end-point. For a parameter to act as a surrogate end-point or surrogate parameter, the surrogate must be a correlate of the true clinical outcome and it must fully capture clinical outcome. Although the first criterion is usually easy to verify, the second is not. But, the extent of drug-induced QT prolongation and the amount of I_{Kr} blockade do not

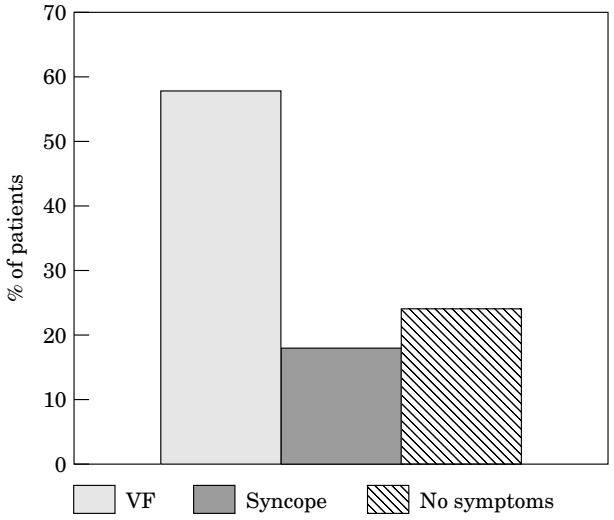

Figure 3 **Clinical presentation of 80 patients with abnormal QT prolongation and TdP studied between 1989 and 1996. Asymptomatic episodes of TdP were detected by Holter monitoring or routine ECG. VF: ventricular fibrillation.**

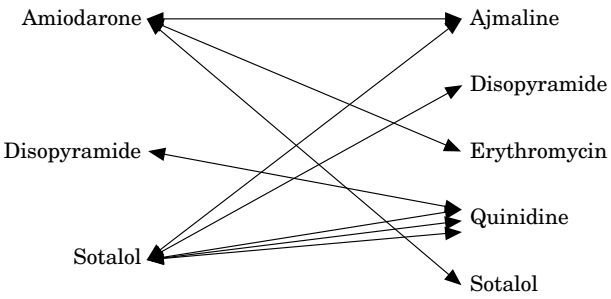

Figure 4 **The problem of 'cross-reactivity': nine patients who developed additional episodes of TdP during subsequent exposure to a repolarization prolonging drug different from the one that initially caused their arrhythmia.**

fulfil the required criteria. There is no linear relationship between the degree of QT prolongation and extent of channel blockade and the likelihood of development of TdP. Amiodarone is a good example for a drug that, although it often causes marked QT prolongation, is only rarely or at least less frequently than expected associated with TdP[16]. It has been suggested that the additional electrophysiological characteristics of amiodarone, such as non-competitive beta-blocking, calcium channel as well as sodium channel blocking effects, might reverse the basic electrophysiological abnormalities that favour TdP[11,17]. Another property which may contribute to an improved safety profile might be the ability of amiodarone to block both the rapidly and the slowly activating component of the delayed rectifier current (I_{Kr} and I_{Ks}). This property of amiodarone has been suggested to account for the lack of significant reverse use dependence of the drug — in other words, a more consistent effect on action potential duration at different heart rates[17]. A good example for the lack of correlation between the extent of channel block (i.e. IC_{50}) and the risk for TdP is verapamil. The drug is a very potent blocker of I_{Kr} with an IC_{50} value close to those of class III agents[18,19]. However, clinical data demonstrating significant QT prolongation are missing. It has been suggested that this may be due to the calcium antagonistic activity; however, it is not clear whether this is true. We know of other calcium antagonistic drugs that potently block the calcium inward current, as verapamil does, but which also rather frequently cause abnormal QT prolongation and TdP (e.g. bepridil)[4].

The torsadogenic potency of drugs — a classification

Recently, several review articles on the problem of drug-induced, acquired long QT syndrome have been published. Most of these articles include listings of drugs which may induce TdP. However, all these listings do not take into account that differences exist in the TdP provoking potency of the individual drugs. Drugs which

Table 3 ***Risk factors that favour the genesis of drug-induced torsade de pointes***

Female gender
Bradycardia
Prolonged baseline QT
Abnormally prolonged QT interval and QTc during drug
T wave lability
T wave morphology changes during drug treatment
Electrolyte disturbances (hypokalaemia, hypomagnesaemia)
High drug doses or concentrations
Rapid intravenous injection/infusion
Use of drugs interfering with the metabolism of drugs known to cause torsade de pointes (e.g. inhibitors of cytochrome P450 enzymes such as erythromycin, ketoconazole, and grapefruit juice)
Cardiac hypertrophy
Diuretic use
Recent cardioversion from atrial fibrillation
Genetic risk factors, i.e. asymptomatic/symptomatic carriers of mutations encoding for K or Na channels

Table 4 The torsadogenic potency of drugs — a classification

Class A (high torsadogenic potency) Drugs which are potent blockers of currents prolonging myocardial repolarization. Action potential prolongation and the induction of early afterdepolarizations have been documented. The drugs are either antiarrhythmic drugs of which the mechanisms of antiarrhythmic drug action is based on prolongation of repolarization or the IC_{50} for this effect is in the same range as the IC_{50} for the therapeutic action. QT prolongation has been documented at therapeutic doses/concentrations and cases of TdP induced by the drug alone (in the absence of concomitant therapy prolonging repolarization and/or hypokalaemia) have been documented.
Class B (medium high torsadogenic potency) Drugs which prolong myocardial repolarization (i.e. cardiac action potential duration and QT interval) at higher doses, or at normal doses with concurrent administration of drugs that inhibit drug metabolism (e.g. by inhibiting the cytochrome P450 metabolism). Their IC_{50} for this prolongation of repolarization is above the IC_{50} for the therapeutic effect. Cases of TdP induced by the drug alone have been documented. However, TdP is usually associated with metabolic inhibition and/or the presence of other risk factors.
Class C (low torsadogenic potency) Drugs that prolong action potential duration and QT interval at high doses/concentrations which are clearly above the therapeutic range. Their effect on repolarization becomes only manifest during overdose, intoxication or in the presence of severe metabolic inhibition. Cases of TdP have been documented. However, in almost all so far available published cases, several factors which are well known to increase the propensity of TdP, i.e. risk factors, were present.
Class D (torsadogenic potential not clear) Drugs which block repolarizing ion currents in vitro but which have so far not been shown to prolong repolarization in other in vitro models (e.g. papillary muscle fibres or isolated hearts) or the concentrations necessary for this effect were far above the clinical concentrations. Prolongation of the human QT interval has not been demonstrated in systematic randomized studies. Cases of TdP in association with treatment with the drug may have been reported. However, the causal relation between the event and the drug is not clear.

may provoke TdP only in the setting of severe intoxication, or overdose, or concommitant medication with drugs also prolonging myocardial repolarization, are mixed up with agents that may induce TdP alone, i.e. in the presence of therapeutic (even sub-therapeutic) concentrations and in the absence of coexisting risk cofactors (Table 3) — in other words, drugs with high and low torsadogenic potenty are listed side by side. In clinical practice, these lists are only of limited value for the treating physician. They may cause more confusion than understanding of the problem of drug-induced TdP. In order to overcome this disaster, we have tried to develop a classification system which takes into account differences in the torsadogenic potency of individual drugs (Tables 4 & 5).

The major criterion for classification is the potency a drug to provoke TdP. When it has clearly been demonstrated and confirmed that a drug alone may cause TdP in one patient, without the presence of coexisting risk factors (e.g. severe hypokalaemia or concommitant therapy with a drug also prolonging repolarization), there is a great chance that it will also do so in other patients. Thus, this particular drug has a significant torsadogenic potency. The provocation of TdP characterizes a drug irrespective of its potency to prolong myocardial repolarization, i.e. the QT interval. However, besides the ability of a drug to induce TdP, additional drug-related properties, i.e. the ability to prolong myocardial repolarization in vitro and in vivo and its capability to provoke early after-depolarizations, which have been considered to play an important role for at least the initiation of TdP, are taken into account. As the classification evaluates the torsadogenic potency of individual drugs, it is superfluous to question whether drug-induced provocation of TdP is a class effect (e.g. a property shared by all agents of a given class such as antihistaminics or makrolide antibiotics) or a specific effect of a few agents within a pharmacological class.

One drawback of such a classification is that published data on the effect on the QT interval, on ion channels (particularly I_{Kr}) and the propensity for induction of early afterdepolarization are not available for all drugs that may cause TdP. However, such a classification must not be considered a static one. It is a dynamic system and the assignment of a drug to a particular drug class may change over time depending on the available knowledge. It is likely that in the near future, more and more detailed studies on the effects of drugs on repolarization parameters will be available making the characterization of the effects of drugs on myocardial repolarization easier.

Treating a patient with a drug that may induce TdP

Except for antiarrhythmic agents, prolongation of repolarization is an unwanted side-effect of drugs. The most effective way to prevent complications of the TdP type is to avoid the use of these drugs. There is almost no disorder that cannot be treated by drugs that do

Table 5 Drugs which may cause QI prolongation andlor TdP[1]

Drug class	Drug	Potency to provoke TdP
Antiarrhythmic drugs	Amiodarone	A
	Ajmaline	B
	Dispyramide	A
	Dofetilide	A
	Ibutilide	A
	Procainamide	A
	Propafenone	B
	Quinidine	A
	Sotalol	A
Antihistaminics	Astemizole	B
	Loratadine	D
	Terfenadine	B
Antibiotics	Clarithromycin	B
	Erythromycin	B
	Pentamidine	B
	Trimethoprim-sulfamethoxazole	C
Antidepressants	Amitryptiline	B
	Imipramine	B
	Doxepin	B
Neuroleptics	Droperidol	B
	Haloperidol	B
	Thioridazine	B
	Sertindole	B
Antimalarial agents	Quinine	B
	Halofantrine	B
Calcium-channel blockers	Bepridil	A
	Lidoflazine	A
Promotility agents	Cisapride	B
Miscellaneous	Amantadine	C

[1]Note: This list is not comprehensive, it gives examples of how drugs may be classified according to the criteria proposed in Table 4.

not prolong repolarization. However, there are many QT prolonging drugs which have certain therapeutic advantages which the physician usually does not want to miss.

In these cases, a systematic approach seems advisable. First of all, the physician prescribing such a drug must be familiar with the problem of drug-induced TdP. Moreover, the physician should also know that the risk for abnormal QT prolongation and TdP varies between patients; while some patients may have a high propensity to the development of drug-associated TdP (patients with one or more of the risk factors listed in Table 3), the risk may be low in others. For example, consider a young male schizophrenic patient with a normal QT level and a structurally normal heart. He is not taking any concommitant medication prolonging the QT interval or medication inhibiting drug metabolism. The patient's history does not give any indication for the presence of a familial long QT syndrome. In such a patients, it is very unlikely that drug-induced TdP will occur, i.e. the risk seems to be almost zero.

If a drug prolonging the QT interval is clinically indicated, it should not be abandoned but administered promptly and with effective dosing. However, it is important not to exceed the recommended dose. The prescribing physician should be aware of potential drug interactions, e.g. the fact that, although normal doses are administered, supra-therapeutic concentrations may be achieved when a drug that inhibits drug metabolism is concurrently given. It is clear that several cases of drug-induced TdP would have been prevented had the potential for pharmacokinetic interactions been known.

It seems reasonable to monitor patients considered to be at an increased risk for TdP by repeated ECG recordings. In the case of antiarrhythmic drugs prolonging repolarization (class A drugs), therapy should be started in hospital. Before start of treatment, an ECG should be recorded in all those patients in whom prescription of a drug which consistently prolongs or is very likely to prolong the QT interval (classes A and B) is planned. This ECG is not intended solely to exclude the presence of abnormal repolarization at baseline, rather it is something which may help to judge changes in repolarization parameters developing during therapy. The potassium level should be checked on a regularly basis in all these patients, particularly when the patient

is taking a potassium-wasting diuretic. In addition, the patient should be warned of the potential problems associated with the use of the drug. It has been suggested that a card listing risk factors (including other agents that prolong the QT interval), precautions and contra-indications for co-prescription should be given to the patient.

Class D agents appear to be relatively safe. However, if symptoms such as dizziness and syncope due to TdP appear, a causative role should be considered. Even these agents should be avoided in patients who can be considered to be at a high risk for drug-induced TdP (i.e. patients with congenital long QT syndrome or patients with a history of drug-induced TdP in the absence of a congenital QT syndrome).

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