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Safety of Non-Antiarrhythmic Drugs that Prolong the QT Interval or Induce Torsade de Pointes

An Overview

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Contents

Abstract 263
1. Mechanisms Leading to QT Prolongation 265
2. Listing Non-Antiarrhythmic Drugs with QT Prolonging Potential 265
3. Clinical Significance of Drug-Induced QT Prolongation 270
   3.1 QT and Corrected QT (QTc) Intervals 270
   3.2 Increased QTc and Occurrence of Torsade de Pointes 273
   3.3 Dose-Response Relationship for QT Prolongation 274
   3.4 Interpretation of Plasma Concentrations 274
4. QT Prolongation and Drug Development 275
   4.1 *In Silico* Studies 275
   4.2 Preclinical *In Vitro* and *In Vivo* Studies 278
   4.3 Clinical Studies 281
5. Avoiding Drug-Induced Torsade de Pointes with Marketed Drugs 281
6. Conclusions 282

Abstract

The long and growing list of non-antiarrhythmic drugs associated with prolongation of the QT interval of the electrocardiogram has generated concern not only for regulatory interventions leading to drug withdrawal, but also for the unjustified view that QT prolongation is usually an intrinsic effect of a whole therapeutic class [e.g. histamine H_1 receptor antagonists (antihistamines)], whereas, in many cases, it is displayed only by some compounds within a given class of non-antiarrhythmic drugs because of an effect on cardiac repolarisation. We provide an overview of the different classes of non-antiarrhythmic drugs reported to prolong the QT interval (e.g. antihistamines, antipsychotics, antidepressants and macrolides) and discusses the clinical relevance of the QT prolonging effect. Drug-induced torsade de pointes are sometimes considered idiosyncratic, totally unpredictable adverse drug reactions, whereas a number of risk factors for their occurrence is now recognised. Widespread knowledge of these risk factors and implementation of a comprehensive list of QT prolonging

drugs becomes an important issue. Risk factors include congenital long QT syndrome, clinically significant bradycardia or heart disease, electrolyte imbalance (especially hypokalaemia, hypomagnesaemia, hypocalcaemia), impaired hepatic/renal function, concomitant treatment with other drugs with known potential for pharmacokinetic/pharmacodynamic interactions (e.g. azole antifungals, macrolide antibacterials and class I or III antiarrhythmic agents). This review provides insight into the strategies that should be followed during a drug development program when a drug is suspected to affect the QT interval. The factors limiting the predictive value of preclinical and clinical studies are also outlined.

The sensitivity of preclinical tests (i.e. their ability to label as positive those drugs with a real risk of inducing QT pronglation in humans) is sufficiently good, but their specificity (i.e. their ability to label as negative those drugs carrying no risk) is not well established. Verapamil is a notable example of a false positive: it blocks human ether-a-go-go-related (HERG) K^+ channels, but is reported to have little potential to trigger torsade de pointes. Although inhibition of HERG K^+ channels has been proposed as a primary test for screening purposes, it is important to remember that several ion currents are involved in the generation of the cardiac potential and that metabolites must be specifically tested in this *in vitro* test. At the present state of knowledge, no preclinical model has an absolute predictive value or can be considered as a gold standard. Therefore, the use of several models facilitates decision making and is recommended by most experts in the field.

In the past few years, several non-antiarrhythmic drugs were withdrawn from the market because of reports of torsade de pointes, a polymorphous ventricular tachyarrhythmia that may cause syncope and degenerate into ventricular fibrillation.[1,2] These events were associated with the ability of a given compound to prolong the duration of the cardiac action potential, hence the QT interval of the surface electrocardiogram (ECG). Although prolongation of the QT interval by non-antiarrhythmic drugs is not an unusual finding, potentially fatal arrhythmias such as torsade de pointes are uncommon and are unlikely to occur during phase I-III clinical trials, when relatively small numbers of subjects are exposed to the investigational drug. Thus, QT prolongation has become a surrogate marker of cardiotoxicity and has received increasing regulatory attention.[3] However, the most important, unresolved problem is that there is no consensus on the degree of QT prolongation to be considered clinically significant, as we will discuss in section 3.

Several classes of drugs have been implicated in prolongation of the QT interval and, in each case, the question arises whether this is a class effect [e.g. shared by all agents of a given pharmacological class such as histamine H_1 receptor antagonists (antihistamines)] or a specific effect of a few molecules. Indeed, in several cases (e.g. antihistamines, fluoroquinolones, serotonin 5-HT_4 receptor agonists), it has been shown that the ability to affect cardiac repolarisation is not necessarily related to the main pharmacological action.[4-10] Thus, it becomes important for prescribers to identify those agents within a therapeutic class carrying a pro-arrhythmic risk and to be aware of risk factors for the occurrence of torsade de pointes.

A recent article in *Drug Safety*[11] has already reviewed some aspects of drug-induced QT prolongation, with particular emphasis on methodological issues related to measurement of the QT interval, correction formulas, design of clinical trials. The present article will provide a general overview,

focussing on some aspects that were not previously covered.

1. Mechanisms Leading to QT Prolongation

The QT interval reflects the duration of individual action potentials in cardiac myocytes. Thus, prolongation of the action potential duration (APD) will result in a prolonged QT interval. Cardiac APD is controlled by a fine balance between inward and outward currents in the plateau repolarisation phase. Since outward K^+ currents, especially the delayed rectifier repolarising current, I_K (which is the sum of two kinetically and pharmacologically distinct types of K^+ currents: a rapid, I_{Kr}, and a slow, I_{Ks}, component), play an important role during plateau repolarisation and in determining the configuration of the action potential, small changes in conductance can significantly alter the effective refractory period, hence the APD. Drugs that prolong the APD by blocking K^+ currents are used as antiarrhythmics (class III antiarrhythmics) for their ability to terminate reentry phenomena.[12] For additional mechanisms leading to prolongation of the APD see the previous review.[11]

Several studies support the notion that the basic mechanism by which many drugs that are not used for the treatment of arrhythmias prolong the QT interval is related to blockade of potassium currents. For instance, several antihistamines, antibacterial macrolides, fluoroquinolones and antipsychotics were shown to inhibit the rapid component of the delayed rectifier K^+ current (I_{Kr}) in electrophysiological studies and to block potassium channels encoded by the human ether-a-go-go-related gene (HERG).[7,13-17] Although I_{Kr} is the most extensively studied,[18] action on other potassium currents (e.g. the slow component of the delayed rectifier current I_{Ks}, the transient outward current I_{to}, the ultra-rapidly activating delayed rectifier current I_{Kur}, and the inward rectifier I_{K1} current) may also account for a prolongation of the APD.[19-25] The overall relevance of a given current may depend on the type of ion channels expressed in different parts of the heart (e.g. atrium *vs* ventricle), on the species, on the pathophysiological condition (low *vs* high heart rate; ischaemic *vs* normal myocardium).

The HERG K^+ channel can be expressed in homologous and heterologous cells in order to assess the potency of a drug [inhibitory concentration $(IC)_{50}$] as a class III antiarrhythmic. Thus, IC_{50} values in mammalian or human systems are important to gain insight into the mechanism leading to QT prolongation, although extrapolation to the clinical setting must carefully consider concentration ranges[1] and possible additional pharmacological effects. These complementary pharmacological actions may increase (e.g. hypokalaemia induced by diuretics, β-adrenoceptor agonists, insulin or amphotericin B) or, in some cases, decrease (e.g. amiodarone, verapamil)[11,26] the proarrhythmic potential *in vivo*. Antidepressants are another example of drugs with complex pharmacological actions on K^+, Na^+ and Ca^{2+} channels leading to variable effects on the QT interval *in vivo*, depending on the animal species and experimental model.[27-31]

Concerning the specificity of QT prolongation as a marker of an effect on cardiac repolarisation, it should be kept in mind that the duration of the QT interval may be affected by both the velocity of repolarisation and ventricular conduction velocity. For instance, as a result of Na^+ channel blockade, class I antiarrhythmics and local anaesthetics can reduce ventricular conduction velocity, cause widening of the QRS complex and therefore prolong the QT interval[32-34] (for a discussion, see Sheridan[35]). Cocaine is another example of a drug with multiple targets: it has a local anaesthetic action and recent reports also indicate a blocking action on HERG K^+ currents.[36,37] Indeed, cocaine has been associated with QT prolongation/torsade de pointes.[38-41]

2. Listing Non-Antiarrhythmic Drugs with QT Prolonging Potential

In the recent past, QT prolongation by a non-antiarrhythmic drug was still considered as a pharmacological curiosity with little clinical impact,

but the number of fatalities associated with these drugs has rapidly changed this view. Although for many non-antiarrhythmic drugs the incidence of torsade de pointes is a rare event (less than one in 100 000),[42] even a low risk is not justified for those drugs whose benefit remains a matter of debate.

Several authors suggest that, in order to increase awareness among prescribers that many non-antiarrhythmic drugs can affect cardiac repolarisation, a list of QT prolonging drugs should be made available and regularly updated.[43]

A common problem of these lists is that it is difficult for the clinician to obtain information on the clinical relevance of the QT effect for a single agent. Indeed, some of these drugs have profound effects on the QT interval and may induce torsade de pointes, whereas the effects of others are minor and poorly documented. Especially for case reports, an offending agent is sometimes identified on the basis of questionable clinical evidence, because of the presence of confounding factors. For instance, a large number of case reports identify a drug as the agent responsible for torsade de pointes (or QT prolongation) in the presence of concomitant medication with another QT-prolonging drug or other risk factors (see section 3.1). Thus, mere listing of QT prolonging drugs may generate confusion as to clinical relevance. For example, the possible induction of torsade de pointes by cotrimoxazole (sulfamethoxazole-trimethoprim)[38,44,45] may be perceived by the inexperienced reader to be as well documented as that of astemizole, an antihistamine that is also a potent HERG K^+ channel blocker.[46]

This is the reason why we have recently tried to organise the available information on QT-prolonging drugs at different levels of clinical importance for each compound,[47] in order to help the clinician to track down the relevant literature when deciding whether or not one of these drugs should be administered to a patient. Two main sources of information should be considered about the QT prolonging potential of a drug: the published literature and the documentation submitted to regulatory agencies, which is not publicly available, but is usually reflected by warnings in the summary of the product characteristics.

Table I is an abridged form of the drug list presented in our previous publication[47] and reports, for each agent, the type of evidence supporting an effect on cardiac repolarisation. Evidence has been structured as follows:

- published clinical evidence: occurrence of torsade de pointes, ventricular tachyarrhythmias or QT prolongation;
- published nonclinical evidence: effect on cardiac repolarisation: *in vitro* studies showing I_K inhibition (including HERG K^+ channel inhibition) or prolongation of the APD as well as *in vivo* studies in animals showing QT prolongation;
- official warnings on the proarrhythmic potential considering the following sources: Public Assessment Reports (EPAR) by the European Agency for the Evaluation of Medicinal Products (EMEA), the Physician Desk Reference (PDR) or Dear Doctor Letters by the US Food and Drug Administration (FDA), the British National Formulary (BNF).

Notably, for some drugs only official warnings on QT prolongation are available with no published data, whereas for some older drugs only generic warnings on possible occurrence of arrhythmias are found in spite of published evidence on QT prolongation. In addition, for some agents, only a few (sometimes questionable) case reports of QT prolongation exist (e.g. in the case of fexofenadine only one published case report of life-threatening arrhythmia exists so far[57]) and this brings out our ignorance on their clinical relevance. Our attempt to organise evidence on QT prolongation is only the first step towards the preparation of a drug list detailing, for each drug, the 'proarrhythmic score', which should be based on the weight of the available evidence and be the result of a consensus process. Scoring systems to estimate the risk of development of torsade de pointes are being proposed.[58,59]

Table I. List of non-antiarrhythmic drugs with QT prolonging potential[a]

Drug	Published clinical evidence	Published nonclinical evidence	Official warnings
Gastrointestinal prokinetics			
Cisapride	Yes	Yes	Yes
Domperidone[b]	Yes	Yes	
Antiemetics			
Dolasetron	Yes	Yes	Yes
Granisetron	Yes	Yes	
Ondansetron	Yes	Yes	Yes
Cardiovascular drugs[c]			
Bepridil	Yes	Yes	Yes
Diltiazem		Yes	
Indapamide	Yes	Yes	
Indoramin[b]	Yes		
Isoprenaline (isoproterenol)	Yes	Yes	
Isradipine	Yes	Yes	Yes
Ketanserin	Yes	Yes	Yes
Lidoflazine	Yes	Yes	
Losartan[b]		Yes	
Methoxamine[b]		Yes	
Mibefradil	Yes	Yes	Yes
Nicardipine[b]			Yes
Perhexiline maleate[b]		Yes	
Prenylamine[b]	Yes	Yes	
Triamterene	Yes	Yes	
Trimetaphan[b]	Yes		
Verapamil		Yes	
Vincamine[b]	Yes		
Antibacterials			
Clarithromycin	Yes	Yes	Yes
Clindamycin[b]	Yes		
Cotrimoxazole (trimethoprim-sulfamethoxazole)[b]	Yes	Yes	
Erythromycin	Yes	Yes	Yes
Gatifloxacin		Yes	Yes
Grepafloxacin	Yes	Yes	Yes
Levofloxacin	Yes	Yes	
Moxifloxacin	Yes	Yes	Yes
Roxithromycin	Yes	Yes	
Sparfloxacin	Yes	Yes	Yes
Spiramycin[b]	Yes		
Antimycotics for systemic use[d]			
Fluconazole	Yes		
Ketoconazole	Yes	Yes	
Agents used in general anaesthesia			
Enflurane	Yes	Yes	
Fentanyl[b]		Yes	
Halothane	Yes	Yes	

Continued next page

Table I. Contd

Drug	Published clinical evidence	Published nonclinical evidence	Official warnings
Isoflurane	Yes	Yes	
Ketamine[b]		Yes	
Pentobarbital (pentobarbitone)[b]		Yes	
Propofol[e]	Yes	Yes	
Sevoflurane	Yes	Yes	
Sufentanil	Yes	Yes	
Thiopental	Yes	Yes	
Opioids			
Levacetylmethadol			Yes
Methadone[b]		Yes	
Pethidine (meperidine)[b]		Yes	
Antimigraine agents			
Naratriptan[b]			Yes
Sumatriptan[b]			Yes
Zolmitriptan[b]			Yes
Antipsychotics			
Amisulpride[b]	Yes		Yes
Chlorpromazine	Yes	Yes	Yes
Clozapine[f]	Yes	Yes	
Droperidol	Yes	Yes	Yes
Haloperidol	Yes	Yes	Yes
Mesoridazine[b]			Yes
Olanzapine[b]	Yes	Yes	Yes
Pimozide	Yes	Yes	Yes
Prochlorperazine[b]	Yes		Yes
Quetiapine[b]	Yes		Yes
Risperidone		Yes	Yes
Sertindole	Yes	Yes	Yes
Sultopride[b]	Yes	Yes	Yes
Thioridazine	Yes	Yes	Yes
Tiapride[b]	Yes		
Trifluoperazine[b]		Yes	
Ziprasidone	Yes		Yes
Zotepine[b]			Yes
Antidepressants			
Amitriptyline	Yes	Yes	Yes
Citalopram[b]	Yes	Yes	
Clomipramine[b]	Yes		
Desipramine	Yes		Yes
Doxepin	Yes	Yes	
Fluoxetine[b]	Yes		Yes
Imipramine	Yes	Yes	
Maprotiline[b]	Yes		
Mianserin[b]	Yes	Yes	
Nortriptyline	Yes	Yes	
Paroxetine[b]	Yes		
Protriptyline[b]	Yes		
Trazodone[b]	Yes		
Venlafaxine[b]			Yes

Table I. Contd

Drug	Published clinical evidence	Published nonclinical evidence	Official warnings
Zimeldine[b]	Yes	Yes	
Antimalarials			
Chloroquine	Yes		
Halofantrine	Yes	Yes	Yes
Mefloquine	Yes		Yes
Quinine	Yes		Yes
Anti-asthmatics[g]			
Fenoterol	Yes		Yes
Procaterol	Yes		
Salbutamol (albuterol)	Yes		Yes
Salmeterol	Yes		Yes
Antihistamines			
Astemizole	Yes	Yes	Yes
Azelastine[b]			Yes
Cetirizine[f]		Yes	
Chlorpheniramine[b]		Yes	
Clemastine[b]		Yes	
Cyproheptadine[b]		Yes	
Diphenhydramine-dimenhydrinate[b]	Yes	Yes	
Ebastine[f]	Yes	Yes	
Emedastine[b]			Yes
Epinastine[b]		Yes	
Fexofenadine[f]	Yes		
Loratadine[f]		Yes	
Mizolastine	Yes	Yes	Yes
Oxatomide[b]	Yes		
Promethazine[b]	Yes	Yes	
Pyrilamine[b]		Yes	
Terfenadine	Yes	Yes	Yes
Miscellanea			
Amantadine[b]	Yes		
Antimony sodium gluconate[b]	Yes		
Arsenic trioxide	Yes		Yes
Bupropion[b]	Yes		
Chloral hydrate[b]	Yes		
Dexfenfluramine[b]		Yes	
Famotidine[b]	Yes		
Felbamate[b]			Yes
Fenoxedil[b]	Yes		
Foscarnet[b]			Yes
Fosphenytoin[b]			Yes
Glibenclamide (glyburide)[b]	Yes	Yes	
Hydroxyzine[b]	Yes	Yes	
Mitoxantrone[b]		Yes	
Octreotide[b]			Yes
Papaverine (intracoronary)[b]	Yes		
Pentamidine	Yes		Yes
Probucol	Yes		Yes

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Table I. Contd

Drug	Published clinical evidence	Published nonclinical evidence	Official warnings
Radiographic contrast media	Yes	Yes	
Ritanserin[b]	Yes		
Sildenafil[b]		Yes	
Tacrolimus	Yes	Yes	
Tamoxifen (high doses)	Yes	Yes	Yes
Terodiline	Yes	Yes	
Tizanidine[b]			Yes
Vasopressin[b]	Yes		
Vesnarinone[b]		Yes	

a The list includes drugs with QT prolonging potential on the basis of three different criteria: (i) published clinical evidence associating the drug with the occurrence of torsade de pointes, ventricular tachyarrhythmias or QT prolongation; (ii) published non-clinical evidence for an effect on cardiac repolarisation: *in vitro* studies showing I_K inhibition (including HERG K^+ channel inhibition) or prolongation of the action potential duration as well as *in vivo* studies in animals showing QT prolongation; and (iii) official warnings on the proarrhythmic potential considering the following sources: European Public Assessment Reports by the European Agency for the Evaluation of Medicinal Products, the Physician Desk Reference or Dear Doctor Letters by the US Food and Drug Administration, the British National Formulary. The full reference list is reported in De Ponti et al.[47]

b Poorly documented.

c Cardiovascular drugs have complex pharmacological actions on cardiac electrophysiology and it would be simplistic to consider evidence in a single preclinical model as an absolute warning signal (verapamil is a classical example of a false positive in the test for inhibition of HERG K^+ currents, see section 4.2). For these drugs, the overall benefit/risk balance may turn out to be favourable in spite of preclinical tests reporting an effect on cardiac repolarisation. Finally, it should be noticed that the final effect on the QT interval may result from both direct cardiac effects and actions on other targets (for instance, diuretics induce hypokalaemia). Of course, the table does not include drugs having the main indication as antiarrhythmics (e.g. amiodarone, azimilide, dofetilide, ibutilide, procainamide, propafenone, quinidine, sotalol).

d Azole antifungals must be considered for two reasons: (i) they are potent inhibitors of drug metabolism, hence the strong potential for drug interactions; (ii) they may affect cardiac repolarisation *per se* and induce torsade de pointes.[8,48-51]

e Propofol has variable effects on the corrected QT interval[52-55] and is reported to shorten the QT interval in patients with idiopathic long QT syndrome.[56]

f QT prolonging potential debated or very low (see sections 2 and 3.1 for the cases of fexofenadine and ebastine, respectively).

g Apart from their cardiovascular action, β_2-adrenoceptor agonists may induce hypokalaemia (a known risk factor for torsade de pointes).

HERG = human ether-a-go-go-related gene.

From the regulatory point of view, a consensus process may promote a balanced benefit/risk assessment of each QT-prolonging, non-antiarrhythmic drug on the basis of pharmacoepidemiological, safety and efficacy data. It seems to us particularly important that an independent opinion be available to avoid overinterpretation of QT data among competing products for marketing reasons. Thus, clinicians should become more knowledgeable about the terminology as well as the methodology of studies assessing this cardiac safety parameter.

3. Clinical Significance of Drug-Induced QT Prolongation

3.1 QT and Corrected QT (QTc) Intervals

QT prolongation is a convenient end-point to assess, but it is important to recognise that it is only a surrogate marker of cardiotoxicity and there is no consensus on the degree of QT prolongation that becomes clinically significant.[3] Although the risk of developing torsade de pointes is proportional to the degree of QT prolongation (a QTc or, at low

heart rates, an uncorrected QT interval value greater than 500 msec raise clear concerns about the potential to induce torsade de pointes),[3,60] actual occurrence of torsade de pointes and ventricular fibrillation depends on a number of concomitant risk factors that may be associated in a single patient (table II). Indeed, there are reported cases of torsade de pointes in patients with apparently normal QT interval.[61]

To further complicate the issue, no standard exists even for QT measurement itself. Several authors have already drawn the attention to the inherent difficulties involved in accurate measurement of the QT interval. These are summarised in table III.

The QT interval is a dynamic physiological variable depending on multiple factors such as cardiac cycle length (heart rate), autonomic nervous system activity, age, gender, circadian rhythm,

Table II. Risk factors for the occurrence of torsade de pointes

Risk factors	Examples and references
Subject-related	
Female gender	Two thirds of the cases of drug-induced torsade de pointes occur in women[62,63]
Congenital long QT syndrome; QTc > 440 msec (high risk with QTc > 500 msec); increased QT dispersion	Congenital long QT syndromes.[64] Heterogeneity of cellular repolarisation in long QT syndromes[65]
Clinically significant bradycardia (<50 beats/min)	Sinus bradycardia, atrioventricular block[59]
History of clinically significant heart disease	Myocardial hypertrophy, heart failure[66,67]
Electrolyte imbalance	Hypokalaemia, hypomagnesaemia, hypocalcaemia
Endocrine disorders and altered nutritional states	Hypothyroidism, diabetes mellitus,[68,69] starvation, alcoholism
Cerebrovascular diseases	Stroke, intracranial and subarachnoid haemorrhage
Hypothermia	[70,71]
Impaired drug metabolism/clearance	Impaired hepatic[a] or renal function[73]
	Poor metabolisers:
	CYP2D6 polymorphism (e.g. enhanced levels of thioridazine[b] ring sulfoxide)[74,75]
	CYP2C19 polymorphism (suggested higher incidence of terodiline-induced cardiotoxicity)[76]
Drug-related	
Use of antiarrhythmic drugs (class I or class III)	Blockade of K^+ channels is the main target of class III drugs
	Some class I drugs (e.g. quinidine) may display also class III properties (i.e. blockade of HERG K^+ channels)
Use of non-antiarrhythmic drugs listed in table I[c]	Cisapride, erythromycin, terfenadine, thioridazine, sertindole, etc.
Drug interactions	Pharmacodynamic interactions: e.g. administration of a drug listed in table I associated with antiarrhythmics (class I and III) or drugs inducing electrolyte imbalance (e.g. risk of hypokalaemia with diuretics, insulin, β-adrenoceptor agonists, amphotericin B, etc.)
	Pharmacokinetic interactions[d,e]: e.g. administration of a drug listed in table I associated with a drug that inhibits its metabolism:
	Cisapride or terfenadine associated with CYP3A4 inhibitors (e.g. antibacterial macrolides, azole antifungals, HIV protease inhibitors, grapefruit juice)
	Some antidepressants or antipsychotics associated with CYP2D6 inhibitors[f] (quinidine, halofantrine, fluoxetine, paroxetine, thioridazine, terbinafine)

a QT interval is frequently prolonged in patients with cirrhosis, regardless the aetiology of the disease.[72]

b Thioridazine is a substrate and an inhibitor of CYP2D6 as well as an HERG K^+ channel blocker.

c The different drugs may widely differ in their proarrhythmic potential even within the same therapeutic class.

d Some of these are actually mixed pharmacodynamic/pharmacokinetic interactions: e.g. ketoconazole and thioridazine are respectively CYP3A4 and CYP2D6 inhibitors, but may *per se* inhibit HERG K^+ channels.

e A drug may be a substrate for multiple isoenzymes: the fact that two drugs are substrates for the same isoenzyme does not necessarily mean that there is a clinically significant drug interaction.

f Interactions involving CYP2D6 are less well documented than those involving CYP3A4. It should be noted that quinidine, halofantrine and thioridazine are also HERG K^+ channel blockers.

CYP = cytochrome P450 enzyme; **HERG** = human ether-a-go-go-related gene; **QTc** = corrected QT interval.

Table III. Problems encountered in obtaining reliable measurements of drug-induced changes of the QT interval

Patient variability	High intraindividual variability in QTc values (circadian variation; law of regression to the mean)[77,78]
	High interindividual variability in QTc values (males *vs* females; infants *vs* adults)
	Unknown prevalence in the general population of patients carrying silent mutations in the ion channels responsible for cardiac repolarisation (these subjects have normal QTc value, but reduced repolarisation reserve)[79,80]
	Variability in the individual metabolic capacity for a given drug
Measurement of QT interval	Definition of the end of the T wave.[11,81] Changes in T wave morphology and occurrence of U waves (these may be important warning signs and precede the occurrence of torsade de pointes)
	Errors in manual measurement in QT interval especially at low paper speed[82]
	Variability in the heart rate (need to correct the QT value for heart rate)
	Lack of a strict definition of normal and abnormal QTc values
	Lack of reliable correlation between readings from Holter recordings and standard ECG
	Lack of standardisation of automated ECG readings (computerised methods are not reliable)[11,81,83]
Pharmacokinetics	Timing of ECG measurements with respect to peak/steady state drug plasma concentrations
	Need to consider plasma concentrations of both parent drug and its significant metabolites (especially if they maintain the ability to block K^+ channels)
	Need for enantioselective methods to monitor plasma concentrations of racemic compounds
Data analysis and interpretation	Different formulas are used to correct duration of the QT interval for heart rate; some formulas may overcorrect at high heart rates and undercorrect at low heart rates (e.g. Bazett's formula)[11,35]
	What is the threshold for a clinically significant change in QTc?
	Definition of the dependent variable (raw QTc interval *vs* maximal QTc interval *vs* maximal QTc change from baseline *vs* area under the QTc interval-time curve *vs* QTc dispersion; see Bonate[84,85]); the use of QT dispersion as the dependent variable is not recommended[81,86,87]
	Statistical power of the study
	A *mean* QTc value during drug treatment is not representative of those patients having important QTc increases (QTc > 500 msec or ΔQTc >60 msec). These outliers must be carefully considered to determine whether their high QTc value is due to chance or they have clinically silent long QT syndrome

ECG = electrocardiogram; **QTc** = corrected QT interval.

plasma electrolyte concentrations, genetic variations in ion channels involved in cardiac repolarisation. The determinant that mostly influences the QT interval duration is cycle length (RR interval): the longer the RR interval, the longer the QT interval and vice versa. Therefore, a number of formulas (see Malik[88] for a list) are used to normalise the QT interval for heart rate and obtain a corrected QT interval (QTc), a key issue especially for those drugs that affect heart rate.[11,89] In these formulas, the reference heart rate is usually 60 beats/min (RR interval of 1 sec or 1000 msec). The most used are Bazett's (square root) and Fridericia's (cubic root) formula, respectively: $QTc = QT/RR^{1/2}$ and $QTc = QT/RR^{1/3}$. However, these formulas (especially the Bazett's formula) are not ideal, since the correlation value between QTc and RR is significantly different from zero, showing that QTc is still dependent on underlying heart rate. Indeed, the Bazett's formula overcorrects at high heart rates and undercorrects at low heart rates.[11,35] Using this formula, an increase in QTc of 4 to 5 msec may depend on measurement bias, as shown for ebastine.[88]

Derivation of the most appropriate QT correction formula should begin with the assessment of the QT/RR relationship in the population under study. Malik recently tried to obtain a specific formula for his specific dataset using the generic equation $QTc = QT/RR^{\alpha}$, where α was 0.314 in the pooled baseline data, but could vary from 0.161 to 0.417 depending on the individual subject.[88] An important finding was that the QT/RR relationship had a high interindividual variability, but relative intraindividual stability, hence the need to examine the QT/RR relationship in each subject for an accurate assessment of drug effects on the QT inter-

val, especially in phase I/II studies. On the other hand, a simple formula is needed by the clinician to make decisions in everyday clinical practice, in the light of the possible bias of automated analysis. In these circumstances, it is more important to understand the limitations of the correction formula rather than applying multiple formulas. Both the Fridericia's and the Bazett's formula have advantages and disadvantages, although overcorrection at high heart rates may be less problematic using the Fridericia's formula ($\alpha = 0.333$).[88,90-93] The Fridericia's formula, however, requires a more complex calculation (i.e. that of a cubic root, that is not readily available in routine practice), whereas the well-known Bazett's formula is easier to use and may be an acceptable compromise in everyday clinical practice, unless the patient has bradycardia (the risk would be underestimated). Conversely, in case of tachycardia, the Bazett's formula, overcorrecting the QT interval, would lead to consider a patient at higher risk than he actually is (see also Dabrowski et al.[94]).

3.2 Increased QTc and Occurrence of Torsade de Pointes

The likelihood of inducing torsade de pointes increases with increased heterogeneity of repolarisation as well as with an increased probability of early after-depolarisations (EAD). The development of EAD is facilitated both by a reduction in outward currents and/or by an increase in inward currents during phase 2 and 3 of the action potential, since these events will prolong the action potential. The mechanisms leading to EAD have been recently reviewed.[95]

While changes in QTc indicate a drug effect, absolute QTc values have greater prognostic significance for the occurrence of tachyarrhythmias. A QTc value > 500 msec is associated with a significant risk of torsade de pointes. In the EMEA document,[96] the following general guidelines are given on QTc changes (using the Bazett's correction) relative to baseline measurements (see also Bonate and Russell[84] for a discussion):

- individual changes below 30 msec are generally thought unlikely to raise significant concerns about the potential risk of arrhythmias;
- individual changes between 30 and 60 msec are more likely to represent a drug effect and raise concern about the potential risk of arrhythmias;
- individual changes greater than 60 msec raise clear concerns about the potential risk of arrhythmias.

For the evaluation of potential clinical risks associated with QTc changes, individual QTc changes rather than mean values for study populations should be used. Identifying outliers when looking for drug-induced changes in the QT-interval is an important issue. Their high ΔQTc value may be due to chance or they may be silent carriers of the long QT syndrome (subjects with normal QT interval, but carrying subtle genetic defects involving K^+ channels).[79,80,97,98] A recent report proposes dynamic analysis of the QT interval in long QT1 syndrome patients with normal phenotype.[78] Thus, changes in T wave morphology and analysis of TU-wave patterns may be more important than simple measurement of the QT interval.

A number of risk factors for the occurrence of torsade de pointes is now recognised (table II) and their widespread knowledge should help to avoid misprescriptions leading to cardiotoxicity. Women are recognised to have an increased risk.[99-101]

A term that sometimes generates confusion is the definition of drug-induced torsade de pointes as idiosyncratic adverse drug reactions. Roden[102] recently suggested that we should take the 'idio' out of the term 'idiosyncratic' and introduced the concept of repolarisation reserve. He postulated that, in the normal ventricle, there is essentially no risk of developing torsade de pointes because the normal function of the repolarising currents (mainly I_{Kr} and I_{Ks}) ensures a large repolarisation reserve. However, the aforementioned risk factors, by reducing the repolarisation reserve, greatly increase the likelihood of the occurrence of torsade de pointes. Thus, there are clinical circumstances in which torsade de pointes are not so unexpected,

since a patient may have several associated risk factors. A recent study reports that sympathetic activation by a low-salt diet increases the sensitivity to quinidine-induced QT prolongation.[103]

In clinical practice, the use of drugs known to prolong the QT interval is not necessarily associated with an increased occurrence of ventricular arrhythmias, unless high dosage, intravenous route of administration (especially at high injection rates: e.g. erythromycin) or concomitant metabolic inhibitors are used. For instance, a recent study[104] suggests that long term antipsychotic medication at conventional doses does not increase ventricular tachyarrhythmias in patients without cardiac disease, in spite of evidence for prolonged QTc interval and QTc dispersion.[104,105] However, this finding should be interpreted with caution and further clinical studies with adequate statistical power should evaluate the cardiotoxic potential of currently licensed drugs that fall into one of those classes with recognised QT-prolonging effect and guide the benefit-risk assessment of these compounds.

3.3 Dose-Response Relationship for QT Prolongation

The statement that no clear-cut dose-dependency can be observed for drug-induced QT prolongation or occurrence of torsade de pointes sometimes generates confusion. Actually, a recent study[106] confirms that QT prolongation by a wide dose range of dofetilide (a class III antiarrhythmic agent) is dose-dependent. This has also been confirmed with sotalol in a paediatric population.[107] Thus, one can expect dose-dependency for QT prolongation and likelihood of torsade de pointes also with non-antiarrhythmic drugs, especially in case of drug interactions leading to very high plasma levels.[1,102,108] However, the fact that normal plasma levels may be associated with exaggerated increases in the QT interval and even occurrence of torsade de pointes led some to suggest a lack of dose-dependency. Actually, several factors may reduce the repolarisation reserve of a given subject, hence greatly increase the proarrhythmic potential of relatively low plasma levels to such an extent that establishing a dose-response relationship may be impossible, all the more so because drug-induced torsade de pointes are rare events. Thus, QT prolongation by a drug which affects cardiac repolarisation is *per se* dose-dependent (with few exceptions, for drugs having multiple electrophysiological actions[108]), but actual occurrence of torsade de pointes depends on the repolarisation reserve, which is variable among subjects and over time.

Recent *in vitro* studies also show that human K^+ channels with the same mutation detected in subjects with the long QT syndrome and expressed in *in vitro* systems are more sensitive than wild type channels to blockade by certain drugs such as clarithromycin and sulfamethoxazole.[38,109] In silent carriers of the long QT syndrome, drug-induced torsade de pointes may indeed be considered idiosyncratic and unpredictable with the current diagnostic standards, although knowledge of the underlying genetic defect would allow prediction of the possible occurrence of torsade de pointes.

3.4 Interpretation of Plasma Concentrations

A major problem in extrapolating results of *in vitro* electrophysiological studies (IC_{50} for inhibition of K^+ currents, IC_{50} for prolongation of APD, etc.) to the clinical setting is that the pharmacokinetic properties of the compound must be thoroughly studied to allow meaningful comparisons between *in vitro* and plasma concentrations. Plasma concentrations in humans should be considered along with the apparent volume of distribution and the metabolic pathways (metabolites may retain QT prolonging potential). The threshold concentration (or the IC_{50}) for HERG K^+ channel blockade *in vitro* may be higher than peak plasma concentrations achieved at therapeutic doses, but tissue concentrations (specifically, cardiac tissue concentrations) may exceed those found in plasma if the drug has a large volume of distribution. One example is provided by the comparison of pharmacodynamic and pharmacokinetic parameters of terfenadine and astemizole.[1] Terfenadine is readily

metabolised to fexofenadine, which maintains good H_1 receptor blocking activity, but has no effect on the QT interval even at doses well above the therapeutic ones. Unmetabolised terfenadine plasma concentrations are usually below detection limits, but may become detectable in case of pharmacokinetic interactions with drugs known to inhibit the CYP3A4 isoenzyme, in case of overdosage, or concomitant hepatic disease. On the contrary, two of the main metabolites of astemizole (desmethylastemizole and norastemizole) retain the ability to block HERG K^+ currents at nanomolar concentrations.[46] In addition, the large volume of distribution of astemizole (indicating extensive tissue penetration: indeed, the concentration in cardiac muscle is estimated to be more than 100 times as high as the plasma concentration[110,111]) and the long elimination half-life of desmethylastemizole (about 9.5 days) suggest a higher risk of potentially harmful effects on cardiac repolarisation with astemizole than with terfenadine.

4. QT Prolongation and Drug Development

By searching the FDA and EMEA internet sites, one can find several examples of the great impact that the finding of a QT-prolonging effect by non-antiarrhythmic drugs during clinical trials has on drug development (moxifloxacin, gatifloxacin, ziprasidone, levacetylmethadol, etc.). Several reviews are already available on the possible strategies to be used during drug development when a non-antiarrhythmic compound turns out to affect cardiac repolarisation.[2,92,112-115]

The ongoing discussion on the QT prolonging potential of noncardiac drugs and its clinical significance does not allow to provide strict guidelines to standardise procedures to be followed in the study of QT-related toxicity. The EMEA document[96] offers a useful starting point. A similar document by the FDA is awaited. In our opinion, the EMEA document should now be updated especially as regards the formulas used to correct the QT interval and provide at least general guidance on how to define the end of the T wave.

The possible strategies to be followed during development of a new chemical entity are briefly outlined in figure 1. The whole process gives, at every stage, probabilistic answers with the possibility of both false positive and false negative findings. Table IV summarises some of the factors limiting the predictive value of preclinical and clinical studies.

4.1 *In Silico* Studies

Since the finding that a drug candidate affects the QT interval can profoundly impact on its development, this risk should be recognised as early as possible. To this aim, theoretical small molecule structure-activity relationship (SAR), and biomacromolecule structure-function relationship (SFR) studies can play a role.

In principle, to explain a biological event, it is fundamental to identify the macromolecular species directly involved in the process, i.e. the target (usually a protein) responsible for the biochemical cascade leading to the observed effect. In the case of QT prolongation, there is evidence that such targets are K^+ channels, particularly the HERG/MiRP1 channels.[21]

Despite the recognised involvement of HERG K^+ channels in QT prolongation, so far only a few studies have dealt with either the SFR of the channel or the molecular aspects of the drug-HERG interaction. An example can be the interaction of dofetilide with HERG K^+ channels, which was investigated at the molecular level by identifying, through site-directed mutagenesis experiments, amino acid residues involved in the binding of the drug to the channel.[121,122] Another step in the same direction was made considering a few other molecules (MK-499, terfenadine, cisapride), and using alanine-scanning and molecular modeling to build a 3-dimensional (3D) drug-HERG K^+ channels interaction model.[123]

SFR and docking studies such as those mentioned above can lead to an understanding of the binding mode of QT prolonging drugs to a defined target. Indeed, their predictive value in assessing the possibility of a molecule to induce long QT

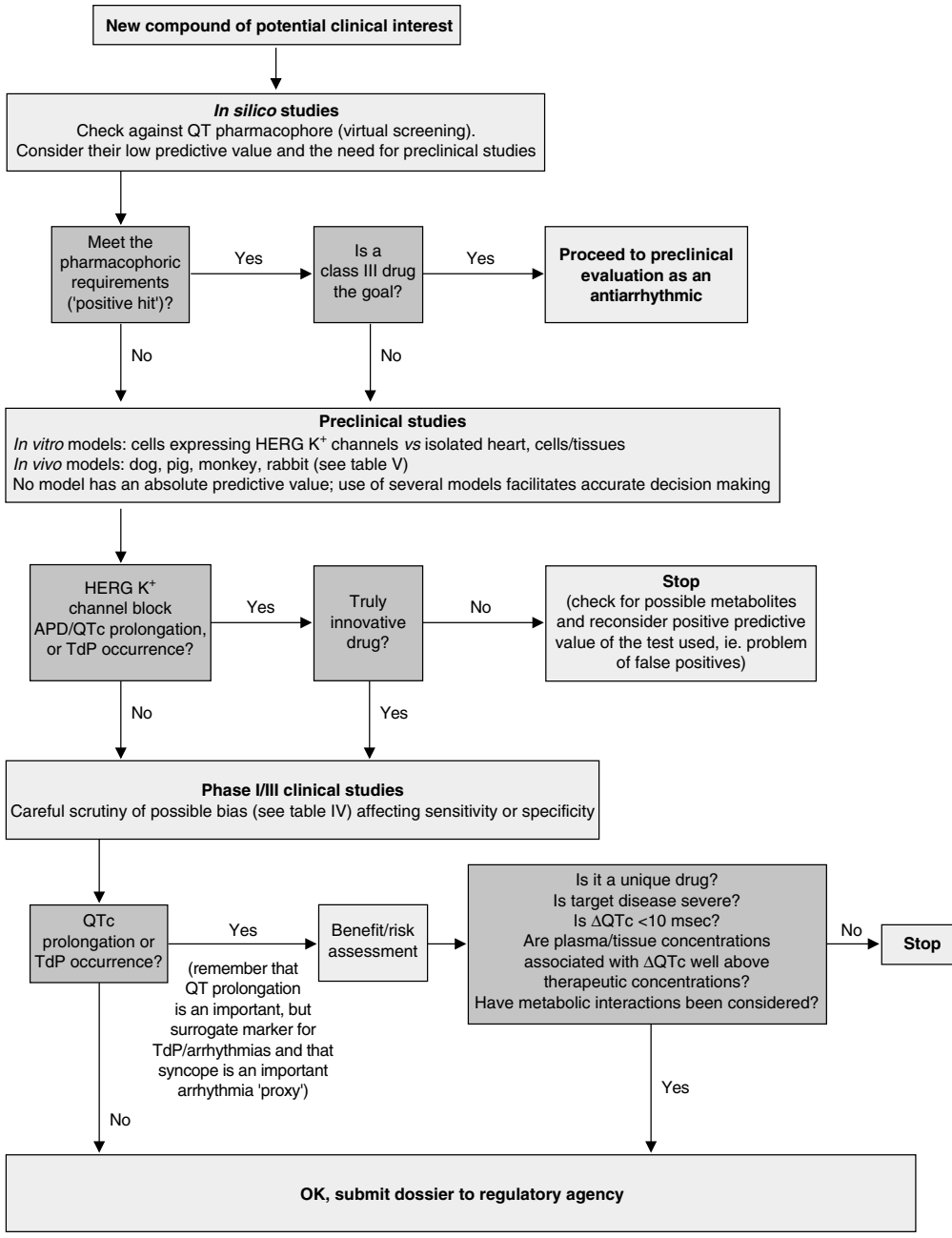

Fig. 1. Proposed strategy for the evaluation of a new chemical entity of potential clinical interest. Although knowledge of the sensitivity and specificity of each preclinical test is important to establish its predictive value, these are not well established so far and no model has been shown to be more predictive than others. Use of different preclinical models offers the best guarantee against the possibility of false negatives and false positives. Investigations on cloned HERG K^+ channels can be considered among primary tests, although they do not provide answers on all currents involved in cardiac repolarisation. The conscious dog model is the most widely used for *in vivo* studies. **APD** = action potential duration; **HERG** = human ether-a-go-go-related gene; **QTc** = corrected QT interval; **TdP** = torsade de pointes.

Table IV. Factors limiting the predictive value of preclinical and clinical studies

In silico studies (sensitivity and specificity not established)	QT prolongation pharmacophore poorly characterised
	Several K^+ channels may be involved in cardiac repolarisation
	In some subjects, single point mutations may lead to HERG K^+ channels with increased affinity for the drug
Preclinical studies (sensitivity good, specificity not well established)	*In vitro* studies
	Activity of metabolites and/or enantiomers must be specifically studied;
	For compounds that are insoluble in water, testing of high concentrations *in vitro* may be restricted
	Species differences in type and distribution of ion channels involved in cardiac repolarisation (species having little plateau phase to cardiac action potential such as the rat are not ideal models; differences in drug metabolism among species)
	HERG K^+ channels are not the only ones responsible for cardiac repolarisation; other repolarising currents as well as drug interaction with different HERG K^+ channel subunits have to be considered[109]
	APD prolongation *per se* is not necessarily associated with proarrhythmia[116]
	Lack of protocol standardisation among laboratories may yield different IC_{50} values (check temperature, frequency of stimulation, K^+ concentration in the medium)[117]
	In vivo studies
	In vivo models require a relatively large sample size (high cost) to pick up small differences in QTc with appropriate statistical power (not suitable for screening)
	When using anaesthetised animals: use of anaesthetics *per se* may affect the QTc interval
	Changes in heart rate require correction; different formulas may optimise correction in different species (table VI)
	Special care must be used to define the end of the T wave: this may be difficult in some species as the dog, having a variable morphology of the T wave. Some breeds may have spontaneous disorders leading to arrhythmic death (normal QT interval and notching of T waves)[118]
Clinical studies	Is the statistical power of the study adequate?
	Which formula is used to correct the QT interval for heart rate? Consider that with some formulas (e.g. Bazett's) a QTc increase of 4 to 5 msec may result from measurement bias[88]
	Were ECGs obtained at the peak of drug effect? Were plasma concentrations above the expected therapeutic range? What is the volume of distribution?[1]
	Was manual or computer-assisted calculation of QTc used? (consider problems in defining the end of the T wave, especially when U waves are present).[119] Remember that computer-assisted analysis of ECG are at present unreliable. Systems for more accurate analysis of TU-wave patterns are being developed.[35,120]
	Were the suggestions by Bonate[84,85] and Malik[11] considered?
	Were all risk factors associated with target patient population (e.g. concomitant liver failure, metabolic interactions) considered?
	Were outliers identified and, if ethically feasible, rechallenged?

APD = action potential duration; **ECG** = electrogardiogram; **HERG** = human-ether-a-go-go-related gene; **IC** = inhibitory concentration; **QTc** = corrected QT interval.

syndrome is strictly connected to the relevance of the studied target towards the clinical phenomenon. The complexity of the cellular events following the drug's interaction with the channel is prohibitively high and it still prevents us from establishing a 'molecular relationship' between channel blockade and QT prolongation. However, to start from the biochemical event underlying the physiological phenomenon is the only way to attempt a mechanistically-based understanding of the clinical syndrome.

A different approach to the molecular interpretation of pharmacological effects is based on the consideration of the characteristics of the bioactive molecules, without taking into account the target. This approach is called 'pharmacophore identifica-

tion', and is centred around the discovery of the 3D structural determinants common to all the molecules displaying the same biological activity.[124] A pharmacophore can thus be defined as the ensemble of the steric and electronic features associated with a given pharmacological property.

The pharmacophore approach was followed earlier in the field of QT prolonging drugs in an attempt to define a general structural frame accounting for the activity of selective class III antiarrhythmic agents.[125] Moreover, a recent study of the conformational and electronic characteristics of two drugs (ebastine and terfenadine) allowed to identify some structural determinants responsible for the different behaviour of the two molecules with respect to their QT-related cardiotoxicity.[126]

These studies can lead to SAR models which do not rely on the knowledge of the biological target, but are only related to the physicochemical properties of the drug molecules. Through the use of appropriate procedures based on suitable activity data, it is also possible to attempt the construction of quantitative (statistically-based) models of SAR (QSAR) to predict the activity of molecules not yet tested. To this aim, one can look for correlations between activity and parameters describing the physicochemical properties of the molecules: lipophilicity, acidity/basicity or molecular volume can be such descriptors.[127] In addition, more sophisticated tools are available to integrate the pharmacophore and the QSAR approaches, and to develop the so-called 3D-QSAR models.[128]

For the purpose of an early assessment of the QT-prolonging potential of drug candidates, pharmacophore-based virtual screening procedures can be considered at present as the most appropriate ones, in terms of both rapidity and objectiveness. As structural information on the target (HERG or other K^+ channel) becomes available from x-ray crystallographic studies, it will eventually allow to refine the pharmacophore, or to directly perform 'structure-based virtual screening using pharmacophore constraints'.[129] As outlined above, in the latter case, the relevance of the macromolecular target needs to be unambiguously assessed before it can be included in virtual screening protocols.

A final caveat regards the need to carefully validate any putatively predictive model to be used for the *in silico* screening of new molecules, since, at the present state of knowledge, the results of studies assessing the structure-activity relationship should not be used as an absolute criterion for a 'go/no go' decision in drug development. In this context, validation of a theoretical tool implies to accurately estimate the pharmacological activity of molecules for which that activity is unambiguously determined. To this end, the most reliable test system for the QT prolonging effect must be identified and a database of drugs known to induce such an effect must be available. The drug list presented in table I might constitute the starting set to attempt the formulation of a pharmacophoric hypothesis.

4.2 Preclinical *In Vitro* and *In Vivo* Studies

Several reviews are available on preclinical models,[2,11,92,112-114] which will not be discussed in detail here. Table V provides a brief synopsis of the most widely used preclinical models.

The sensitivity of preclinical tests (i.e. their ability to label as positive those drugs with a real risk of inducing QT prolongation in humans) is sufficiently good,[132,139,140] but their specificity (i.e. their ability to label as negative those drugs carrying no risk) is not well established. Verapamil is a notable example of a false positive: it blocks HERG K^+ channels, but is reported to have little potential to trigger torsade de pointes.[117,141,142]

Determining the IC_{50} value for inhibition of K^+ conductance in native or cloned HERG channels has been proposed as a primary test for screening purposes;[112,117] however, it is important to remember that several ion currents are involved in the generation of the cardiac action potential and that metabolites must be specifically tested in this *in vitro* test.

At the present state of knowledge, no preclinical model has an absolute predictive value or can be considered as a gold standard (see, for instance Gintant et al.[132]) [table IV]. Therefore, the use of

Table V. Preclinical evaluation of the proarrhythmic potential of QT prolonging drugs

Model	Species (most used)	Advantages[a]
HERG K^+ channels expressed in heterologous or human cells	Human embryonic kidney cells (HEK 293)	Mammalian cell lines are the ideal model for studying an effect on the current underlying I_{Kr}; they allow to use physiological temperatures (37°C) for the human species (for details on experimental conditions see Cavero et al.[92,117])
	Chinese hamster ovary (CHO) cells	
	Oocytes of the amphibian *Xenopus laevis* (not ideal model)	HEK 293, CHO or L cells expressing HERG K^+ channels may be used as a primary test to study the pharmacological activity of a compound;[112,117] inhibition of [^{3}H]-dofetilide binding to HERG channels has also been proposed,[130] but this non-functional assay has some intrinsic limitations[112]
Isolated intact heart (Langendorff preparation)	Rabbit, guinea-pig	It allows screening of a large number of compounds
		Possibility to induce experimental torsade de pointes[131]
Isolated tissues:	Dog, sheep, cat, rabbit, guinea-pig	They allow screening of a large number of compounds and assessment of conditions that favour I_{Kr} block, such as low K^+ concentrations and low stimulation rates
Purkinje fibres[132]		Purkinje fibres are easily accessible and probably the closest representation of M cells
papillary muscle		
transmural wedge preparation of the left ventricle[133]		The transmural wedge preparation allows to detect difference between M cells endo- and epicardial cells (it ensures that the extent of dispersion is explored)
isolated cardiac myocytes		Mouse AT-1 cells: good correlation between IC_{50} values for I_{Kr} block in these cells and IC_{50} values for HERG block in L-cells transfected with HERG[134]
ECG recording in conscious or anaesthetised animals	Dog, pig, monkey (heart rate similar to human heart rate)	Ideal for studying the dose-response relationship for QT interval prolongation taking into account all the pharmacological properties of a compound
	Rabbit, rat, guinea-pig, mouse (species with high baseline heart rate)	The dog model is one of the most widely used; anaesthetised rabbits (especially female rabbits) have also been proposed for high sensitivity[135]
		It provides complementary information with respect to *in vitro* tests (activity of metabolites, measurement of plasma drug concentrations, calculation of the volume of distribution)
		Possibility to induce experimental torsade de pointes[131,136-138]

a Some drawbacks are outlined in table IV.

HERG = human-ether-a-go-go-related gene; **IC** = inhibitory concentration.

several models facilitates accurate decision-making and is recommended by most experts in the field.[142-144]

A recent article[116] provides important insights to understand why lengthening of the APD does not invariably correlate with a proarrhythmic effect (occurrence of EAD and torsade de pointes). The cardiac electrophysiological effects of 702 chemicals were studied in the Langendorff preparation (rabbit perfused heart) and it was found that only those agents that caused lengthening of the APD associated with instability of APD, triangulation and reverse use-dependence were proarrhythmic. Prolongation of the action potential plateau without instability or triangulation was antiarrhythmic rather than proarrhythmic. This observation challenges the use of APD lengthening as a surrogate marker for proarrhythmia and strengthens the notion that the whole spectrum of pharmacological properties of a compound must be considered in order to draw conclusions on its proarrhythmic potential *in vivo*.

Concerning *in vivo* studies, an important issue is the quality of ECG recordings and the methods used for the analysis. A recent survey reports on the current practice in the pharmaceutical industry for assessing the potential for QT prolongation and concludes that 'the majority view in the industry is not necessarily best practice'.[145]

Table VI. Synopsis of some frequently used formulas to correct the QT interval for heart rate (HR) in dogs

Formula	Comments	References
Bazette $QTc = \frac{QT}{\sqrt{RR}}$	Corrects at 60 beats/min; overcorrects at high heart rates, undercorrects at low heart rate. This makes it unsuitable in dogs, which usually have respiratory sinus arrhythmia and considerable variations in conscious heart rate (70-190 beats/min)	118,146,148,150-154
Fridericia $QTc = \frac{QT}{\sqrt[3]{RR}}$	Corrects at 60 beats/min; still overcorrects QT, although to a lesser extent than Bazett's[148]	148,155
Van de Water $QTc = QT - 0.087(RR - 1000) = QT - 87\left(\frac{60}{HR} - 1\right)$	Corrects at 60 beats/min; was found to be superior to Bazett's and Fridericia's formula; using this formula, a sample of eight dogs may be sufficient to detect a 10% change in QTc[154]	146,148
Classen $QTc = QT - 0.084(RR - 500)$	Similar to Van de Water's formula, but corrects at 120 beats/min, i.e. heart that is closer to the mean heart rate of a conscious dog	149
Matsunaga $QTc = \log 600 \bullet \frac{QT}{\log RR}$	Corrects at 100 beats/min, i.e. heart that is closer to the mean heart rate of a conscious dog	156,157
Spence $\log QTc = \log QT - \beta(\log HR - \log HRm)$	Analysis of covariance can be used to derive a flexible method to correct the QT interval, but requires a larger sample size than other formulas in order to determine the degree of correction (β). HRm is the reference heart rate.	148

The dog is the most popular species for *in vivo* studies.[145] This preference seems to be justified by the fact that the heart rate range is closer to that of humans (smaller animals have much higher baseline heart rates) and by the similarities in ionic determinants of Purkinje fibre and ventricular action potentials. However, it is important to remember that T wave morphology and RR intervals are highly variable in dogs and must be analysed by an expert veterinarian. Investigators should be aware that the accuracy of the Bazett's or Fridericia's formulas to correct the QT interval for heart rate is most uncertain in animals because formulas used in humans cannot be readily applied to animals. So far, the dog is the only species in which the problem of QT correction has been investigated by several groups.[146-150] Table VI provides a synopsis of the different formulas that may be applied and should be considered when designing studies in this species. Although it is now recognised that the Bazett's formula is even more unsatisfactory in dogs, it should be noted that at present none of the proposed formulas can be endorsed as the ideal formula, because each has advantages and drawbacks (see Spence et al.[148]). If accuracy of the correction formula is a particular concern for the investigator, one could attempt to derive a heart rate correction algorithm for each animal from the QT/RR relationship.

Since the conscious dog model is relatively expensive and is not suitable for screening a large number of compounds, calculation of the sample size to have sufficient statistical power is an important issue. With the Van de Water's formula, it has been suggested that a sample size of five to eight dogs is sufficient to detect changes in QTc of 10%.[154] Finally, these studies should always include a positive control (i.e., a drug known to prolong the QT interval)[145] and a vehicle-injected control (to assess the intrinsic variability of the method used to correct the QT interval).[144]

4.3 Clinical Studies

The main issues related to measurement of the QT interval in clinical studies (quality of ECG recordings, definition of the end of the T wave especially when it merges with a U wave, use of the appropriate correction formulas, appropriate study design) have already been discussed by Malik and Camm.[11] Two other recent reviews[84,85] discuss the options concerning the dependent variable to be measured (raw QTc interval *vs* maximal QTc interval*vs* maximal QTc change from baseline *vs* area under the QTc interval-time curve *vs* QTc dispersion) and the appropriate statistical analysis. Guidelines of the International Society for Holter and Noninvasive Electrocardiology (ISHNE) for electrocardiographic evaluation of drug-related QT prolongation are also available.[158] Some of the common biases of clinical studies are summarised in table IV.

Concerning QT dispersion (calculated as the difference between the longest and shortest QT interval in the 12-lead ECG), this measurement is still mentioned in the EMEA document,[3] for the assessment of repolarisation abnormalities. However, the use of QT dispersion suffers from methodological challenges and recently has been largely discredited.[81,86,87,159-161]

We agree with the strategy proposed by Malik and Camm,[11] which involves carefully designed phase I-II studies, especially for those drugs that appear to have a discrete, albeit small, effect on the QT in preclinical tests. Indeed, phase III studies not always allow to collect as many ECG as actually needed for an appropriate analysis and, in any case, do not have the statistical power to detect rare events such as torsade de pointes.

It should be noticed that a QTc prolongation of <10 msec may be a reason for not granting/withdrawing marketing authorisation (e.g. terfenadine, which induces a mean QTc prolongation of 6 msec, was withdrawn in the US). However, if a truly innovative drug for a severe disease prolongs the QTc interval of <10 msec, plasma/tissue concentrations associated with QT prolongation are well above therapeutic concentrations, and no metabolic interactions have been detected, submission of the dossier to a regulatory agency seems to be justified (figure 1).

In all clinical studies, identifying the percentage of 'outliers' (i.e. those patients having greater QT prolongation) may also be a useful guide to assess risk in subjects treated with a new agent versus comparators.

Finally, an important arrhythmia 'proxy' is the occurrence of syncope, which should be carefully monitored in clinical studies in order to determine whether it is associated with QT prolongation.

5. Avoiding Drug-Induced Torsade de Pointes with Marketed Drugs

A recent drug utilisation study carried out in several countries found significant exposure to non-antiarrhythmic drugs with QT-prolonging potential in the general population. The total amount of these drugs dispensed through community pharmacies in 1998 ranged from 13.1 to 19.6 defined daily doses/1000 inhabitants per day.[162] From total exposure data, however, it is not possible to extrapolate the risk of torsade de pointes in the general population, because of the different proarrhythmic potential among drugs and risk factors that may precipitate QT prolongation into life-threatening arrhythmias. Therefore, widespread knowledge of these risk factors (table II) and of the torsadogenic potential of single agents becomes the key issue to avoid misprescriptions leading to cardiotoxicity.

Since most reports of drug-induced torsade de pointes are related to concomitant risk factors or medications, regulatory intervention often start with 'Dear Doctor Letters' and 'black-box' warnings in the label. Unfortunately, the strategies involving labelling restrictions have repeatedly been shown to have little impact on prescription patterns.[163-165] Thus, the Regulatory Authorities may opt for more effective interventions, such as withdrawal from the market. However, withdrawal must be evaluated against the possible drug bene-

fits, especially in case no valid therapeutic alternatives are available.

When drug withdrawal is not justified, the widespread use of lists of QT prolonging drugs associated with knowledge of risk factors for the occurrence of torsade de pointes could be a more appropriate strategy. Implementation of pharmacy-based software to detect dangerous coprescriptions should be considered, especially in a hospital setting. For instance, McMullin et al.[166] proposed a monitoring system to screen all hospital pharmacy orders and to alert pharmacists and physicians on potentially dangerous drug combinations. They report that dangerous drug combinations with cisapride declined over a 2-year period from 9 to 3%, the mean duration of contraindicated therapy from 4.1 to 1.6 days and the proportion of patient discharge under treatment with a dangerous combination was reduced from 36 to 8%.

Another important step towards more appropriate drug use involves the implementation of lists of QT prolonging drugs (e.g. De Ponti et al.[47] and http://www.torsade.org), which are particularly useful in referral centres for patients with familial forms of the congenital long QT syndrome, who must avoid all possible factors that may reduce their labile repolarisation reserve. In these centres, handouts with brand names of potentially harmful drugs can be prepared on the basis of the aforementioned lists.

6. Conclusions

In the rapidly evolving field of drug-induced QT prolongation no straightforward and absolute rules can be put forward since it must be kept in mind that the benefit/risk balance is unique for each drug. However, a number of principles have emerged in the past few years and are summarised below.

- QT prolongation is an important surrogate marker of poor cardiac safety for any non-antiarrhythmic drug. However, the occurrence of potentially fatal dysrhythmias is the primary issue and there may exist drugs that, for their complex pharmacological profile, prolong the QTc with a relatively low proarrhythmic risk.
- Compounds of the same therapeutic class may profoundly differ as to QT prolonging potential.
- The assessment of the proarrhythmic risk must take into account the metabolism of the suspected agent, since a very low baseline proarrhythmic risk may become clinically important because of drug interactions leading to higher than expected plasma levels.
- An effect on QTc is an important argument to stop drug development, since even a QT prolongation of a few milliseconds may be a reason for not obtaining marketing authorisation by regulatory agencies, unless unique benefits are proven. More accurate screening methods for early detection of possible effects on cardiac repolarisation are now under scrutiny.
- Widespread knowledge of risk factors for the occurrence of torsade de pointes and implementation of detailed lists of QT prolonging drugs is an important step to further reduce the occurrence of this rare, but potentially fatal adverse effect. The development of a 'consensus list' of QT prolonging drugs, structured on the basis of a pro-arrhythmic score, seems to be an important goal in this rapidly changing area. Easy access for prescribers and pharmacists to web-based lists of QT prolonging drugs (with their interactions) will probably contribute to reduce the number of fatalities associated with occurrence of torsade de pointes.
- Although official warnings often have little impact on prescription patterns, it seems logical to suggest harmonisation of warnings in the summary of the product characteristics of drugs known to affect the QT interval. The labelling may indeed provide the basis for developing specific software for the detection of dangerous coprescriptions. Labelling restrictions, however, may be considered an insufficient precaution by regulatory agencies when deciding marketing authorisation of a drug lacking unique benefits.

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