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REVIEW ARTICLE

Fabrizio De Ponti · Elisabetta Poluzzi
Nicola Montanaro

Organising evidence on QT prolongation and occurrence of *Torsades de Pointes* with non-antiarrhythmic drugs: a call for consensus

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Abstract *Background*: The growing list of non-antiarrhythmic drugs associated with QT prolongation and the relevant regulatory interventions have generated concern for two reasons. First, QT prolongation is sometimes viewed as an intrinsic effect of a whole therapeutic class (for example, 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. Second, drug-induced *Torsades de Pointes* are still considered *idiosyncratic*, totally unpredictable adverse drug reactions, whereas a number of risk factors for their occurrence is now recognised.
Objectives: In order to increase awareness among prescribing physicians that many non-antiarrhythmic drugs can affect cardiac repolarisation, we would like to propose a comprehensive and updated list of QT-prolonging drugs that should be a starting point to maintain a "consensus list" to be periodically updated.
Methods: The drug list was generated by performing a Medline search, by using published lists as starting points to retrieve the relevant references quoted in each article and by considering the International Registry for Drug-induced Arrhythmias maintained by the Georgetown University and mainly based on the FDA approved labelling.
Results: The drug list presented in this paper: (1) includes virtually all non-antiarrhythmic drugs with QT-prolonging potential, (2) organises the available information on each drug at different levels of clinical relevance and (3) is as up-to-date as possible in order to provide a fast track for the clinical pharmacologist to retrieve the original publications.
Conclusions: This list should be considered as a starting point to call for consensus on: (1) the criteria used to generate the list, (2) possible ways to implement the use of this list as a quick reference for clinicians, for instance by providing a "proarrhythmic score" for each drug, and (3) inclusion/exclusion of a given agent into the list on the basis of evidence that may not be available to us.

Keywords Adverse drug reactions · QT interval · Cardiac arrhythmias

F. De Ponti (✉) · E. Poluzzi · N. Montanaro
Department of Pharmacology, University of Bologna and Interuniversity Research Centre for Pharmacoepidemiology, Via Irnerio 48, 40126 Bologna BO, Italy
E-mail: deponti@biocfarm.unibo.it
Tel.: +39-051-2091805
Fax: +39-051-248862

Introduction

The literature on QT prolongation and proarrhythmic risk of non-cardiac drugs has grown exponentially in the past decade and a recent review in this journal has already discussed some basic and clinical aspects of the problem [1]. The growing list of non-antiarrhythmic drugs associated with QT prolongation and the relevant regulatory interventions have generated concern for two reasons. First, QT prolongation is sometimes viewed as an intrinsic effect of a whole therapeutic class (for example, 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 [1, 2]. Second, drug-induced *Torsades de Pointes* (TdP) are still considered *idiosyncratic*, totally unpredictable adverse drug reactions. However, Roden [3] 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 TdP because the normal function of the repolarising currents (mainly I_{Kr} and I_{Ks}) ensure a large repolarisation reserve. In addition, he drew attention to the many well-known risk factors (such as female gender, hypokalaemia, bradycardia, genetic defects underlying the congenital long QT syndrome) which, by reducing the repolarisation reserve, greatly increase the likelihood of the occurrence of TdP. Thus, there are clinical circumstances in which TdP are not so unexpected.

A recent editorial in the British Medical Journal [4] underscores the low level of awareness among prescribing physicians that many drugs can cause QT prolongation and suggests that QT prolonging non-cardiac drugs should be listed and regularly updated in national formularies. Lists of such drugs are indeed available in several recent reviews [5, 6, 7, 8], but all share a common problem. A footnote to the list provided in the Policy Conference Report of the European Society of Cardiology [6] acknowledges that it derives *"from what is effectively a non-controlled review of the literature. Hence, some of the drugs listed have profound effects on QT prolongation and on induction of TdP, and others have minor effects whose documentation is in some instances questionable and not clearly related to the drugs given as opposed to an intercurrent condition. The list is presented, then, to indicate the diversity of drugs and effects cited. However, the reader is urged to review the literature on any of these drugs before making decisions that relate to their administration."*

To obviate at least in part to the above limitation, the present article aims at recapitulating the evidence so far available by proposing a list that should: (1) include virtually all non-antiarrhythmic drugs with QT-prolonging potential, (2) organise the available information on each drug at different levels of clinical relevance and (3) be as up-to-date as possible (January 2001) in order to provide a fast track for the clinical pharmacologist to retrieve the original publications.

Some problems are encountered to achieve the above aims. First, the available information is often contradictory and, especially for case reports, an offending agent is identified on the basis of questionable clinical evidence. The most striking observation is that a large number of case reports identify a drug as the agent responsible for the occurrence of TdP (or QT prolongation) in the presence of concomitant medication with another QT-prolonging drug (see, for instance, Kamochi et al. [9]). Thus, mere listing of QT-prolonging drugs may generate confusion as to clinical relevance. For example, the possible induction of TdP by sulphamethoxazole/trimethoprim (which is indeed reported in isolated cases [10, 11, 12]) may be perceived by the inexperienced reader to be as well documented as that of astemizole, an antihistamine that is at least as potent as class III antiarrhythmic agents in blocking HERG K^+ channels [13]. Since a detailed discussion of each QT-prolonging agent would require a textbook, we thought that organising the available information at different levels of clinical importance for each drug would help the clinician to track down the relevant literature when deciding whether or not one of these drugs should be administered to a patient. Identifying those agents for which only a few (sometimes questionable) case reports exist may also bring out our ignorance on their clinical relevance.

Second, we realise that reviewing the world literature to create a complete and updated list is actually a very difficult task. Therefore, in this article we will try to use broad criteria to organise the available evidence and propose a list of QT-prolonging, non-antiarrhythmic drugs. This list should be considered as a starting point to call for consensus (see last section). When considering the drug list that will be proposed, it is important to keep in mind that QT prolongation per se does not necessarily mean that the risk-benefit balance of a non-antiarrhythmic drug is negative. Since the final balance depends on a number of factors that must be weighed very carefully [1] and the various drugs do differ as to QT-prolonging potential, our list should not be considered as a "blacklist of dangerous drugs": in our opinion, only for some agents should the risk-benefit profile receive formal reassessment in the light of recent information about effects on cardiac repolarisation.

Defining criteria to organise the available information

In Table 1, we propose three main criteria (each divided into two subcriteria) to organise the available evidence on the proarrhythmic potential of QT-prolonging drugs that are not used as antiarrhythmics and discuss the relevant advantages and drawbacks for each criterion. These criteria are then applied to prepare the drug list presented in Table 2, which includes drugs with QT-prolonging potential, with the exception of those agents that are used as antiarrhythmics.

The first criterion: clinical evidence for occurrence of TdP or QT prolongation

The first criterion used to generate the drug list was the existence of published clinical evidence associating the drug with the occurrence of TdP, ventricular tachyarrhythmias or QT prolongation. Occurrence of TdP (usually associated with QT prolongation) and QT prolongation alone were used as separate criteria (Ia and Ib, respectively), because QT prolongation is a surrogate marker of cardiotoxicity (used for regulatory purposes because of the rare occurrence of drug-induced TdP) and there is no consensus on the degree of QT prolongation that becomes clinically significant. For many drugs that have received regulatory approval recently, a mean QT prolongation < 10 ms in clinical trials generated a lot of debate (as can be verified at the FDA and the EMEA Internet site), although this degree of QT prolongation is not usually considered significant in current clinical practice.

The first criterion has a significant publication bias, since evidence provided by positive studies (sometimes only questionable case reports) are not balanced by negative, prospective studies, because these are difficult to perform. Studies with appropriate statistical power to exclude QT prolongation require a large number of subjects and, of course, using drug-induced TdP as an end-point in prospective studies is not always feasible for ethical reasons. To further complicate the issue, evidence

Table 1 Criteria used to organise the available evidence on the proarrhythmic potential of QT-prolonging non-antiarrhythmic drugs. (*TdP* Torsades de Pointes)

Criteria	Advantages	Drawbacks
I. Published clinical evidence:	Published clinical trials represent a major source of clinical evidence and help to evaluate the clinical relevance of in vitro/animal studies	Publication bias: many published case reports on occurrence of TdP are inadequate (some seem to ignore that a concomitant medication could affect cardiac repolarisation or do not take into account known risk factors for the occurrence of TdP); negative studies are difficult to perform
a. Clinical studies and/or case reports associating the drug with the occurrence of TdP/ventricular tachyarrhythmias b. Clinical studies reporting QT prolongation	Case reports/series are early clinical signals of cardiotoxicity during phase IV and may allow identification of silent carriers of the long QT syndrome	QT prolongation is a surrogate marker of cardiotoxicity and there is no consensus on the degree of QT prolongation that may be viewed as clinically significant
II. Published non-clinical evidence on effects on cardiac repolarisation:	Useful information to study the arrhythmogenic mechanism of the drug suspected to cause ventricular tachyarrhythmias by reducing the repolarisation reserve	Several currents (not only I_{Kr}) control cardiac repolarisation; drugs that delay ventricular conduction velocity may also prolong the QT interval (by widening the QRS complex)
a. In vitro studies showing HERG K^+ channel blockade (i.e. inhibition of human I_{Kr})	May help to distinguish whether the effect on cardiac repolarisation is a class effect or is displayed only by some agents within a therapeutic class	No model has an absolute predictive value
b. In vitro studies showing I_K inhibition or prolongation of the action potential duration, or in vivo studies in animals showing prolongation of the QT interval	Useful for the preclinical assessment of drugs suspected to affect cardiac repolarisation	Discrepancies among laboratories for different experimental procedures may lead to different IC_{50} values for HERG K^+ channel inhibition (see Table 3) Considering the IC_{50} reported in vitro, it is difficult to extrapolate the clinical relevance at therapeutic plasma concentrations (tissue rather than plasma concentration should be considered)
III. Official warnings in the labelling (including official warnings issued by EMEA, FDA) on:	Easily accessible source of information for the prescribing physician, often based on data that are not available in the published literature	Official warnings cannot be taken as the gold standard to assess clinical relevance because:
a. QT prolongation or occurrence of TdP b. Cardiac arrhythmias as adverse effect	Often reflects a clinically significant effect on cardiac repolarisation	They are not always updated according to current knowledge They may reflect precautions taken at the time of marketing authorisation (for example, they may consider QT prolongation as a class effect rather than an effect displayed only by some compounds within a non-antiarrhythmic class) Of the lack of harmonisation of the official labelling among different countries

that a compound does not prolong the mean QT interval in a study population does not rule out the possibility that a drug-induced TdP may occur in a single individual (for example, a silent carrier of the long QT syndrome, see below). In addition, several of the published case reports or case series, especially with psychotropic agents, are inadequate: some of them involve extreme overdosage and cannot be directly extrapolated to routine clinical practice. In others [9, 14], the authors seem to ignore that concomitant medications may also affect the QT interval, so that it is impossible to establish a causal relationship between a single drug and occurrence of TdP (for a recent review on causality assessment of suspected adverse drug reactions, see [15]; for examples on the complexity of this issue see Woosley and Darrow [16] and Shivkumar [17]).

To generate the drug list, we performed a Medline search using the following keywords: long QT syndrome – chemically induced; torsades de pointes – chemically induced; (torsad*[ab] OR qt[ab]) AND *drug name* [ab]. We also used published lists [1, 5, 6, 7, 8] as starting points to retrieve the relevant references quoted in each article. Finally, we considered the International Registry for Drug-induced Arrhythmias, mainly based on the FDA approved labelling, maintained by the Georgetown University (www.torsades.org).

Table 2 Non-antiarrhythmic[a] drugs with QT-prolonging potential. Sources of information for criterion III: EMEA, European Public Assessment Reports or Committee for Proprietary Medicinal Products Opinions; PDR, Physician Desk Reference or Dear Doctor Letters from FDA (resulting in labelling changes); BNF, British National Formulary (number 39, March 2000); SPC, Italian Summary of the Product Characteristics

Drug	Criterion I		Criterion II		Criterion III	
	Clinical evidence		Non-clinical evidence		Official warnings	
	a	b	a	b	a	b
Gastrointestinal prokinetics						
Cisapride (withdrawn or available on a limited access basis for QT-related problems)	[37, 38, 39, 40]	[41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52] [53, 54][b]	[55, 56, 57, 58] (6.5–44.5 nmol l^{-1})[c]	[59, 60, 61, 62, 63, 64, 65, 66]	EMEA, PDR, BNF, SPC	
Domperidone	[67, 68] ?		[69] (162 nmol l^{-1})	[69]		
Antiemetics						
Dolasetron		[70, 71, 72]	[73] (5.95 μmol l^{-1})		PDR	
Granisetron		[74] [75][b]	[73] (3.73 μmol l^{-1})	[76]		PDR
Ondansetron		[70, 74]	[73] (0.81 μmol l^{-1})	[76, 77]	PDR	BNF, SPC
Cardiovascular drugs[d]						
Bepridil		[78, 79]	[80, 81] (550 nmol l^{-1})	[82, 83]	PDR	
Diltiazem			[84] (17.3 μmol l^{-1}) [80, 81][b] (*lower concentrations*)			PDR, SPC
Indapamide	[85] (hypokalaemia)			[86]		PDR (premature ventricular contractions), SPC
Indoramin	[87] ?	[88]				
Isoprenaline (isoproterenol)	[89]	[90, 91]		[92, 93]		BNF
Isradipine		[94] [95, 96][b]		[97] [98][b]	See www.torsades.org	
Ketanserin	[99]	[100, 101, 102]		[103, 104, 105]	SPC	
Lidoflazine	[106, 107]			[108]		
Losartan		[109][b]	[110] (1 μmol l^{-1} inhibit HERG by ca 23%)	(for completeness see [111])		PDR
Methoxamine				[112, 113]		BNF (as a class effect)
Mibefradil (no longer marketed)		[114]	[80, 81] (1.43 μmol l^{-1})	[115]	PDR	
Nicardipine					PDR (see www.torsades.org)	
Perhexiline maleate			[116, 117] (7.8 μmol l^{-1})	[117, 118]		
Prenylamine	[119] ?			[120]		
Triamterene		[121]		[122, 123]		PDR
Trimetaphan	[124]					
Verapamil		[95][b]	[80, 81, 84] (143–830 nmol l^{-1})			SPC
Vincamine	[125]					

Antibacterials					
Clarithromycin	[9, 23, 126, 127]	[42, 128]	[23] (720 μmol l^{-1} wild-type; 240 μmol l^{-1} mutated channel)	[129] [130][b]	SPC
Clindamycin	[131]				
Erythromycin	[132, 133, 134, 135, 136, 137]	[138, 139]		[133, 140, 141, 142, 142, 144, 145, 146]	BNF, PDR
Gatifloxacin		[147][b]	[148] (130 μmol l^{-1})	[149]	PDR
Grepafloxacin (withdrawn for QT-related problems)	[150]	[151]	[148, 152] (50–104 μmol l^{-1})	[149, 153]	PDR, BNF, SPC
Levofloxacin	[154, 155] (see also [156, 157])		[148] (915 μmol l^{-1})	[158][b]	
Moxifloxacin		[159, 160] (see also [161])	[148, 152] (103–129 μmol l^{-1})	[153, 162]	PDR, SPC
Roxithromycin		[163, 164] (with amiodarone) [165]		[129, 146]	
Sparfloxacin		[165, 166, 167, 168]	[148, 152] (18–34.4 μmol l^{-1})	[149, 153, 158, 169, 170]	EMEA, PDR
Spiramycin	[171, 172]				
Sulphamethoxazole/trimethoprim	[10, 11]	[12]	[12]		
Antimycotics for systemic use					
Fluconazole	[173]				BNF (metabolic interactions)
Ketoconazole		[174, 175]	[176] (49 μmol l^{-1})	[177]	BNF (metabolic inter actions)
Agents used in general anaesthesia					
Enflurane		[178, 179]		[180]	BNF, SPC
Fentanyl				[181]	PDR
Halothane	[182]	[178, 183] [179, 184][b]		[180, 185, 186] (for completeness, see [187])	BNF, SPC
Isoflurane		[178, 184, 188]		[180]	SPC
Ketamine				[189, 190, 191]	SPC
Pentobarbital				[192, 193] (for completeness, see [194, 195])	
Propofol		Variable effects on QTc [196, 197] [198, 199, 200][b] (shortens the QT interval in patients with idiopathic long QT syndrome)		[190, 201] (see also [202])	
Sevoflurane		[203]		[183]	
Sufentanyl		[188, 204]		[181]	
Thiopental		[179, 205, 206, 207]		[141, 201, 202, 208, 209]	SPC

Table 2 (Contd.)

Drug	Criterion I		Criterion II		Criterion III	
	Clinical evidence		Non-clinical evidence		Official warnings	
	a	b	a	b	a	b
Opioids						
Levacetylmethadol					EMEA, PDR	
Methadone				[210]		
Pethidine (meperidine)				[211]		
Antimigraine agents						
Naratriptan					PDR	
Sumatriptan					PDR	
Zolmitriptan					PDR	
Antipsychotics						
Amisulpride		[212]			BNF	
Chlorpromazine	[213, 214]	[215]	[216] (1.47 μmol l^{-1})	[217]	SPC	BNF
Clozapine		[218]		[219, 220]		PDR
Droperidol	[221, 222]	[223, 224]	[225] (32.2 nmol l^{-1})	[219, 225]	See www.torsades.org	BNF (under evaluation January 2001)
Haloperidol	[223, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235]	[236]	[237] (ca 1 μmol l^{-1})	[220, 238]	PDR	BNF, SPC
Mesoridazine					PDR (see www.torsades.org)	
Olanzapine		European Public Assessment Report (EMEA)		[220]	EMEA	
Pimozide	[130, 239, 240]	[239, 241]	[218] (18 nmol l^{-1})	[130]	BNF, PDR, SPC	
Prochlorperazine	[17] ???	[242]			PDR	BNF (as a class effect)
Quetiapine		[243]			PDR, BNF	
Risperidone				[220]	PDR, BNF	
Sertindole (marketed authorisation suspended in Europe for QT-related problems)		[244, 245]	[246] (14 nmol l^{-1})	[220]	EMEA, BNF, SPC	
Sultopride	[247, 248]			[219, 247]	SPC	
Thioridazine	[249, 250]	[215, 224, 251, 252, 253]	[216, 254] (1.07–1.25 μmol l^{-1})	[219, 254, 255, 256]	PDR, BNF	SPC
Tiapride	[257]					
Trifluoperazine				[217]		PDR, BNF (as a class effect)
Ziprasidone		[258]			PDR	
Zotepine					BNF	
Antidepressants						
Amitriptyline	[259, 260, 261]	[262]	[216, 263, 264] (3.26–10 μmol l^{-1})	[265, 266, 267, 268, 269] [32][b]	BNF, SPC	
Citalopram		[270, 271] [272][b]		[271]		
Clomipramine	[214, 273]	[274]				BNF (as a class effect), SPC

Desipramine		[274, 275]			PDR	SPC
Doxepin	[276]	[277]		[267]		BNF
Fluoxetine	[278] [279] ?	[277][b]			PDR	
Imipramine		[280]	[263] (3.4 μmol l^{-1})	[267, 281]		BNF, SPC
Maprotiline	[282] (questionable case report)	[283, 284] ?				BNF (as a class effect), SPC
Mianserin	[285]	[286] (questionable case report)		[269]		BNF (as a class effect)
Nortriptyline		[287, 288]		[267]		BNF, SPC
Paroxetine		[289] (questionable case series)				
Protriptyline	[290]					BNF (as a class effect)
Trazodone	[291] (with amiodarone)	[280, 292]				BNF (as a class effect)
Venlafaxine					PDR, SPC	
Zimeldine (no longer marketed)	[293]	[294]		[268]		
Antimalarials						
Artemisinin and derivatives (no official labelling yet available)		[295, 296, 297] [298, 299][b]		[300]		
Chloroquine	[301]	[302] [303][b]				PDR (ECG changes), BNF (ECG changes)
Halofantrine	[304, 305]	[306, 307, 308, 309]	[310] (196.9 nmol l^{-1})	[305, 311, 312]	BNF, [313], see www.torsades.org	
Mefloquine		[307, 314, 315]		[312, 316][b] (however, mefloquine potentiates the QT prolonging effect of halofantrine)	PDR	
Quinine[e]		[242, 297, 317, 318] [319][b]			See www.torsades.org	
Antiasthmatics						
Fenoterol		[90, 320] (associated with hypokalaemia)			BNF (as a class effect)	
Procaterol		[321]				
Salbutamol (albuterol)		[90, 320, 322] (associated with hypokalaemia)			PDR, BNF	
Salmeterol		[323, 324] [322] (associated with hypokalaemia) [325][b]			PDR, BNF (as a class effect), SPC	
Antihistamines						
Astemizole (withdrawn for QT-related problems)	[326, 327, 328, 329, 330, 331, 332, 333, 334]	[335]	[13, 336, 337] (1–48 nmol l^{-1})	[338, 339, 340, 341, 342, 343, 344, 345]	PDR, BNF, SPC	
Azelastine					PDR (see www.torsades.org)	
Cetirizine		[346][b]	[336][b]	[340] [347] (high concentrations) [343][b]		
Chlorpheniramine			[337] (20 μmol l^{-1})	[337, 338, 344, 348, 349]		

Table 2 (Contd.)

Drug	Criterion I		Criterion II		Criterion III	
	Clinical evidence		Non-clinical evidence		Official warnings	
	a	b	a	b	a	b
Clemastine				[344, 348]		BNF (as a class effect)
Cyproheptadine				[348]		
Diphenhydramine/dimenhydrinate	[350] (widening of the QRS, massive poisoning) [351]	[352, 353]	[2, 337] (21.5 μmol l^{-1})	[348, 353] [337, 344, 354][b]		
Ebastine		[355] (for discussion see [174, 356, 357, 358])	[359] (ca 3 μmol l^{-1})	[360, 361, 362] (for discussion see: [177, 363, 364, 365, 366]) [344][b]		
Emedastine					EMEA	
Epinastine			[367] (>100 μmol l^{-1})	[361] (high concentrations) [345] (high dose) [368][b]		
Fexofenadine	[369] (for comments, see [370])	[371, 372][b]	[373][b]	[344, 374][b]		
Loratadine		[375, 376][b] (see also [16]	[377, 378] (0.173–2.8 μmol l^{-1}) [379, 380][b]	[379][b]		SPC
Mizolastine		[381] [382, 383][b]	[384] (0.35–3.4 μmol l^{-1})		EMEA, SPC	
Oxatomide		[12]		[344][b]		
Promethazine	[385]			[348]		
Pyrilamine				[338]		
Terfenadine (withdrawn in the USA for QT-related problems)	[374, 386, 387, 388, 389]	[390, 391, 392, 393, 394, 395]	[337, 359, 373] (56–350 nmol l^{-1})	[338, 344, 345, 361, 368, 374, 377, 380, 396, 397, 398, 399, 400, 401]	EMEA, PDR, BNF, SPC	
Miscellanea						
Amantadine	[402] ?					PDR
Antimonium		[403]				
Arsenic	[404, 405, 406, 407]	[408]			PDR	
Bupropione		[409] (overdose with intraventricular conduction delay)				PDR
Chloral hydrate	[410]					
Dexfenfluramine				[411]		
Famotidine		[412]				
Felbamate					PDR	
Fenoxedil	[413] ?					
Foscarnet					PDR (ST-T changes)	BNF (ECG changes)
Fosphenytoin					PDR	

Glibenclamide		[414] (see also, for completeness, [415, 416, 417])	[418] (74 μmol l^{-1})			
Hydroxyzine		[419]	[2] (10.7 μmol l^{-1})	[348] [340][b]		
Mitoxantrone[f]				[420, 421]		PDR (cardiac arrhythmias), BNF (cardiotoxicity)
Octreotide					PDR	
Papaverine (intracoronary)	[422]	[423]				
Pentamidine	[424, 425, 426, 427]	[428]			See www.torsades.org	BNF, SPC
Probucol	[429]	[430, 431, 432, 433, 434]			See www.torsades.org	
Radiographic contrast media	[435]	[436, 437, 438, 439]		[112, 440]		
Ritanserin		[441, 442, 443]		[65][b]		
Sildenafil			[444] (100 μmol l^{-1})			EMEA, PDR
Tacrolimus	[445, 446]	[447, 448]		[449, 450, 451, 452]		BNF
Tamoxifen		[453, 454]		[455]	PDR	
Terodiline (withdrawn for QT-related problems)	[456, 457]	[458, 459]		[460, 461, 462, 463, 464, 465, 466]		
Tizanidine					PDR	
Vasopressin	[467, 468]					
Vesnarinone			[469]	[470]		

[a]Drugs that are not used exclusively as antiarrhythmics (for example, verapamil) are included in the present list. Apart from class I and III antiarrhythmics (for example, ajmaline, almokalant, amiodarone, aprindine, azimilide, bretylium, clofilium, disopyramide, dofetilide, ibutilide, N-acetylprocainamide, procainamide, propafenone, quinidine, sematilide and sotalol), a few other drugs not listed in this table can prolong the QT interval and/or induce TdP. Local anaesthetics, as a result of Na^+ channel blockade, can cause widening of the QRS complex (hence, the associated QTc prolongation) after intravenous or intracoronary administration [471, 472]. These effects, however, are usually observed in safety studies using high doses and a route of administration that is not the one intended for clinical use. Therefore, local anaesthetics were not included in the present list. Cocaine, which also has a local anaesthetic action, has been associated with QT prolongation/TdP [12, 473, 474, 475] although comedication/drug abuse make interpretation of available reports difficult. Nicotine may affect cardiac repolarisation by blocking K^+ channels [476]. Finally, QT prolongation and ventricular arrhythmias are described with organophosphate insecticide poisoning [477]

[b]These references refer to negative studies (i.e. reporting no effect) and have been added for the sake of completeness

[c]The values reported in this column represent the IC_{50} reported for inhibition of HERG K^+ channels

[d]The cardio vascular drugs presented in this list have complex pharmacological actions on the heart. For instance, verapamil (a racemic drug) is used as an antihypertensive but is also a class IV antiarrhythmic agent. Its spectrum of pharmacological actions cannot be covered in this table

[e]Tonic water may contain small amounts of quinine

[f]Mitoxantrone is structurally related to anthracyclines, which are well known for their cardiac toxicity, although mechanisms are still under investigation. Several reports have associated anthracycline treatment with QT prolongation and episodes of arrhythmias [478, 479, 480, 481, 482]

Table 3 Preclinical evaluation of the proarrhythmic potential of QT-prolonging drugs

Model	Species (most used)	Advantages	Drawbacks
ISOLATED INTACT HEART (Langendorff preparation)	Rabbit, guinea-pig	It allows screening of a large number of compounds	Failure to see prolongation of the action potential duration does not provide complete security
		Possibility to induce experimental TdP [483]	Activity of metabolites must be specifically studied
			For compounds that are insoluble in water, testing of high concentrations may be restricted
ISOLATED TISSUES, Purkinje fibres, Papillary muscle, Transmural wedge preparation of the left ventricle [93], Isolated cardiac myocytes	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	Species differences concerning type and distribution of ion channels involved in cardiac repolarisation (species having little plateau phase to cardiac action potential such as rat or mouse are not ideal models)
		Purkinje fibres are easily accessible and probably the closest representation of M cells	
		The transmural wedge preparation allows to detect difference between M cells endo- and epicardial cells (it ensures that the extent of dispersion is explored)	
ECG RECORDING in conscious or anaesthetised animals	Dog, pig, monkey;	Ideal for studying the dose-response relationship	QTc prolongation is a surrogate marker of cardiotoxicity, with no established threshold, hence high cost because of large sample size required to pick up small differences in QTc with appropriate statistical power (not for screening)
	rabbit, rat, guinea-pig, mouse (species with high baseline heart rate)	It provides complementary information with respect to in vitro tests (activity of metabolites, measurement of plasma drug concentrations, calculation of the volume of distribution)	Changes in heart rate require correction; different formulas may optimise correction in different species
		Possibility to induce experimental TdP [483, 484]	In some models, baseline heart rate may be too high for correct evaluation of QT prolongation
			Differences in metabolism and distribution of ionic channels require caution in extrapolating data to humans
			When using anaesthetised animals, use of anaesthetics per se may affect the QTc interval
HERG K^+ CHANNELS expressed in heterologous or human cells	Human embryonic kidney cells (HEK 293)	Ideal model for studying an effect on the current underlying I_{Kr}	HERG K^+ channels are not the only ones responsible for cardiac repolarisation; other repolarising currents as well as drug interaction with different HERG channel subunits (MiRP1 [23]) have to be considered
	Chinese hamster ovary cells	Mammalian cells allow to use physiological temperatures (37°C) for the human species	Lack of protocol standardisation among laboratories may yield different IC_{50}
	Oocytes of the amphibian *Xenopus laevis*		Activity of metabolites must be specifically studied
	Mouse fibroblasts (C cells)		For compounds that are insoluble in water, testing of high concentrations may be

Table 3 (Contd.)

Model	Species (most used)	Advantages	Drawbacks
			restricted; some compounds may have problems of adsorption to glass/plastic Oocytes of the amphibian *Xenopus laevis*: possible overestimation of the IC_{50} due to the relatively large volume of lipophilic material in the oocyte; experiments carried out at room temperature

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. Class I antiarrhythmics and, in special circumstances, local anaesthetics ([18, 19] and see footnote "a" to Table 2) can reduce ventricular conduction velocity, cause widening of the QRS complex and therefore prolong the QT interval (for a detailed discussion, see [20]).

The statement that no clear-cut dose dependency can be observed for QT prolongation or occurrence of TdP sometimes generates confusion. Actually, a recent study [21] confirms that QT prolongation by a wide dose range of dofetilide (a class III antiarrhythmic agent) is dose dependent. The same holds true for the likelihood of TdP with non-antiarrhythmic drugs, especially in case of drug interactions leading to very high plasma levels ([1, 3, 22]. However, the fact that normal plasma levels may be associated with exaggerated increases in the QT interval and even occurrence of TdP led some to suggest a lack of dose dependency. Actually, several factors may reduce the repolarisation reserve of a given subject and 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 TdP are rare events. Thus, QT prolongation by a drug which affects cardiac repolarisation is per se dose dependent (with few exceptions, such as quinidine, because of its multiple pharmacological actions [22]), but actual occurrence of TdP 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 sulphamethoxazole [12, 23]. Pharmacogenetic studies [24, 25, 26] also raise the issue of silent carriers of the long QT syndrome (subjects carrying subtle genetic defects with normal QT interval, but low repolarisation reserve). In these subjects, drug-induced TdPs 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 TdP.

The second criterion: non-clinical evidence for an effect on cardiac repolarisation

Criterion IIa was introduced on the basis of the widely held concept that most QT-prolonging non-cardiac drugs are potassium channel blockers and inhibit the rapid component of the delayed rectifier current (I_{Kr}). In humans, I_{Kr} is carried by the human ether-à-go-go (HERG) K^+ channel, which can be expressed in homologous and heterologous cells in order to assess the potency of a drug (IC_{50}) in inhibiting this channel. IC_{50} values in mammalian or human systems are important to gain insight into the mechanism of drug action, although extrapolation to the clinical setting must carefully consider concentration ranges [1] and possible additional pharmacological effects. These complementary pharmacological actions may increase (for example, hypokalaemia induced by diuretics, β-adrenoceptor agonists, insulin [27] or amphotericin B) or, in some cases, even decrease (for example, quinidine, see above) the proarrhythmic potential in vivo. Another example of drugs with complex pharmacological actions on K^+, Na^+ and Ca^{++} channels is provided by antidepressants [28, 29, 30, 31]: thus, it is not surprising that their effects on the QT interval in vivo are quite variable, depending on the animal species and experimental model [28, 32].

Since, apart from I_{Kr}, other currents (for example, I_{Ks}, I_{to}) are involved in cardiac repolarisation, criterion IIb considers all in vitro studies showing I_K inhibition or prolongation of the action potential duration as well as all in vivo studies in animals showing prolongation of the QT interval.

Discussing the preclinical evaluation of QT-prolonging drugs and the pros and cons of each model is beyond the scope of this article and the reader is referred to recent reviews [1, 6, 8, 20, 33]. Table 3 provides a brief

synopsis of non-clinical models used to assess the QT-prolonging potential of a compound.

The third criterion: official warnings on the proarrhythmic potential

This criterion has some intrinsic advantages, such as being based on an easily accessible source of information not always available in the published literature. On the other hand, official warnings may not be always updated according to current knowledge or, especially for recently approved drugs, may reflect precautions taken at the time of marketing authorisation, when an effect on repolarisation may be considered as a class effect until there is convincing proof to the contrary. First, we analysed the official labelling (precautions or adverse reaction section or relevant boxed warning) of drugs included into the list on the basis of the literature search and looked for warnings about QT prolongation or possible occurrence of TdP or cardiac arrhythmias. We considered the following sources: European Public Assessment Reports (EPAR) by the EMEA, the Physician Desk Reference (PDR) or Dear Doctor Letters by the FDA, the British National Formulary (BNF, March 2000 edition), the Italian Summary of the Product Characteristics (SPC, latest version). We also searched the EMEA and FDA Internet sites, the PDR and the BNF to identify additional agents whose official warnings on QT prolongation may derive by still unpublished preregistration studies.

Several questions arise on this criterion. First, do all drugs with documented QT-related proarrhythmic risk have official warnings? Indeed, recent experience has shown that regulatory measures were often taken only some time after the QT-prolonging potential (hence, occurrence of TdPs) was reported in the published literature. This is not unexpected for rare events, such as drug-induced TdP, which are detected only after a drug has received marketing authorisation. Second, are official warnings adequate to convey this important safety aspect? Providing information on QT prolongation in a boxed warning rather than in the list of possible adverse reactions has certainly a different impact on the perception of risk by the prescribing physician, and should be used only for some of the agents listed in Table 2. On the other hand, simply including the term ''cardiac arrhythmias'' in the list of adverse reactions (although formally correct) certainly generates a different perception of the type of risk involved. Many QT-prolonging drugs marketed many years ago do not have specific warnings on QT prolongation (for example, first generation antihistamines). Certainly, harmonisation of warnings on QT-related proarrhythmic risk is a desirable goal. In the meantime, we decided that warnings on QT prolongation or occurrence of TdP (criterion IIIa) or arrhythmias (criterion IIIb) should be considered separately. In any case, to avoid inclusion of drugs causing arrhythmias through different or unknown mechanisms, compounds that meet *only* criterion IIIb (and none of the preceding criteria) are not listed in Table 2. However, some agents have warnings on the possible occurrence of arrhythmias and are structurally related to known QT-prolonging drugs (especially psychotropic agents such as substituted benzamides or phenothiazines), although, to the best of our knowledge, no published evidence supports a direct effect on cardiac repolarisation. By contrast, a few recently approved compounds meet criterion IIIa without published evidence of an effect on the QT interval (for example, levacetylmethadol, emedastine, triptans) indicating the great regulatory attention to this matter.

Possible uses of the list and call for consensus

We think that the drug list presented in this article can already provide, in its present form, a useful tool to the clinical pharmacologist, since it draws attention to all the different non-antiarrhythmic drugs with QT-prolonging potential. Promoting awareness of the problem is the first step towards more appropriate drug use. In addition, by presenting an up-to-date, structured and extensive list of original bibliographic sources for each drug (rather than reviews on the topic), it allows the clinician to track down the original information to verify its soundness and validity. Referral centres for subjects with familial forms of the congenital long QT syndrome, who must avoid all possible factors that may reduce their labile repolarisation reserve, could use the information provided in this list to prepare handouts (with relevant brand names).

However, the drug list presented here can certainly be improved by external input since, at the moment, no direct inference can be made on proarrhythmic risk. This is the reason why a consensus process is necessary to structure the list according to clinical relevance, if possible through a ''proarrhythmic score'' that should consider, for each drug, the weight of the available evidence on the proarrhythmic risk versus the expected benefit. This consensus process could start with letters to the Editor addressing the following issues:

1. Criteria used to generate the list: appropriateness of the proposed criteria, inclusion of other criteria
2. Feasibility of a ''proarrhythmic score'' for each drug and items to consider to structure such score
3. Possible ways to implement the use of this list as a quick reference for clinicians
4. Inclusion/exclusion of a given agent into the list on the basis of evidence that may not be available to us.

If this call for consensus generates significant input, the list could be shared through appropriate media, for example, by making it available to specialised discussion groups on the Internet, if possible through the European Association for Clinical Pharmacology and Therapeutics (EACPT) or member societies of the International

Union of Pharmacology (IUPHAR). A panel of experts could work on the present list to achieve consensus and structure it by drug class and proarrhythmic score. This "consensus list" could then to be included in national formularies and regularly updated. Proposals to take an active part on this panel of experts (clinical pharmacologists, cardiologists, clinicians with specific expertise in the use of the different classes of drugs) should be sent to the Editor.

From the regulatory point of view, this consensus process may promote a balanced risk/benefit assessment of each QT-prolonging, non-antiarrhythmic drug on the basis of pharmacoepidemiological, safety and efficacy data. It should also foster discussion on the appropriateness and harmonisation of official warnings on proarrhythmic risk.

A list of QT-prolonging drugs structured according to a proarrhythmic score could also be applied to drug utilisation studies by evaluating the total exposure to drugs with a significant QT prolonging potential. Because of the large number of drugs involved, evaluating total exposure to such agents in the general population will probably contribute to assess the magnitude of the problem, especially outside of the hospital setting [34, 35].

Finally, from a basic scientific perspective, the drug list presented here could be used as an inventory by the medicinal chemist and the molecular pharmacologist to identify apparently unrelated molecules that share a high affinity for the HERG K^+ channel and hence are potent class III antiarrhythmics. Studying structure–activity relationships and the site(s) of drug interaction with HERG K^+ channels (see, for example, [36]) will certainly impact on drug development and perhaps allow, in the near future, *in silico* screening of new chemical entities to test for possible, unwanted interference with cardiac repolarisation.

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