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REVIEW

Drug-induced QT interval shortening: potential harbinger of proarrhythmia and regulatory perspectives

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ATP-dependent potassium channel openers such as pinacidil and levcromakalim have long been known to shorten action potential duration and to be profibrillatory in non-clinical models, raising concerns on the clinical safety of drugs that shorten QT interval. Routine non-clinical evaluation of new drugs for their potential to affect cardiac repolarization has revealed that drugs may also shorten QT interval. The description of congenital short QT syndrome in 2000, together with the associated arrhythmias, suggests that drug-induced short QT interval may be proarrhythmic, and an uncanny parallel is evolving between our appreciation of the short and the long QT intervals. Epidemiological studies report an over-representation of short QT interval values in patients with idiopathic ventricular fibrillation. Therefore, as new compounds that shorten QT interval are progressed further into clinical development, questions will inevitably arise on their safety. Arising from the current risk-averse clinical and regulatory environment and concerns on proarrhythmic safety of drugs, together with our lack of a better understanding of the clinical significance of short QT interval, new drugs that substantially shorten QT interval will likely receive an unfavourable regulatory review unless these drugs fulfil an unmet clinical need. This review provides estimates of parameters of QT shortening that may be of potential clinical significance. Rufinamide, a recently approved anticonvulsant, illustrates the current regulatory approach to drugs that shorten QT interval. However, to further substantiate or confirm the safety of these drugs, their approval may well be conditional upon large-scale post-marketing studies with a focus on cardiac safety.
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Abbreviations: AF, atrial fibrillation; APD, action potential duration; CHMP, Committee for Medicinal Products for Human Use; CPMP, Committee for Proprietary Medicinal Products; ECG, standard 12-lead surface electrocardiogram; EMEA, European Medicines Agency, London; FDA, Food and Drug Administration, USA; hERG, human ether-a-go-go related gene; ICH, International Conference on Harmonization; LQTS, long QT interval syndrome; MHRA, Medicines and Healthcare products Regulatory Agency; SQTS, short QT interval syndrome; TdP, torsade de pointes; VF, ventricular fibrillation

Introduction

Our understanding of clinical outcomes associated with drug-induced prolongation of QT interval owes much to the discovery of, and the clinical outcomes associated with, congenital forms of long QT interval syndrome (LQTS). In compliance of the evolving regulatory requirements over the last decade or so, sponsors have been routinely investigating new drugs for their potential to prolong cardiac repolarization. In the course of these investigations, a number of drugs have been found to actually shorten the action potential duration (APD) and/or QT interval as well as being profibrillatory. At first, this effect observed in non-clinical studies was treated as an idiosyncrasy of questionable clinical significance and generally received little further attention. However,

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recent clinical description of congenital forms of short QT interval syndrome (SQTS) and the arrhythmias associated with these syndromes have begun to raise concerns regarding the potential proarrhythmic consequences of drugs that may shorten QT interval in man.

Moreover, the description of SQTS is beginning to unravel an uncanny parallel in our appreciation of the clinical significance of the short and the long QT intervals such that it would be prudent not to dismiss but rather to explore the clinical safety implications of drug-induced QT shortening. In order to highlight this parallel and to initiate a debate on the frequency and the potential clinical significance of drug-induced QT shortening, the author retraces briefly the gradual evolution of our understanding and concerns about drug-induced QT prolongation. This review summarizes the pertinent literature on congenital forms of short QT interval and their associated proarrhythmia and the epidemiological data that link proarrhythmia with short QT interval. It then goes on to discuss some drugs that shorten APD and/or QT interval and are found to be profibrillatory. Finally, the review considers potential regulatory implications and approaches to the assessment and approval of new drugs that are found to have these electrophysiological effects in non-clinical or clinical studies. Data on the effect of rufinamide (a recently approved triazole anticonvulsant) on QT interval are also summarized to illustrate the current pragmatic but cautious approach of regulatory authorities in evaluating drugs that shorten QT interval. This review also provides the author's estimates of parameters of QT shortening that may be of potential clinical significance.

Evolution of concerns regarding drug-induced QT interval prolongation

In one of the earliest analysis of a large series of cases ($n = 168$) of QT interval prolongation reported by Bellet and Finkelstein (1951), the only drug to appear in the list of causes was quinidine (in eight patients). In six patients, the cause was unknown and the authors concluded, 'Future studies may make it possible to place them in their proper categories'. These authors did not have to wait too long for the probable classification of their six cases. Not long after their review, Jervell and Lange-Nielsen (1957) described a congenital form of LQTS in a family in which four of the six children were affected by deaf-mutism, prolongation of QT interval and sudden death. This seminal report was later followed by a number of other similar reports (Levine and Woodworth, 1958; Romano *et al.*, 1963; Ward, 1964). When reporting nine additional cases, Fraser *et al.* (1964a,b) suggested a genetic relationship between the syndromes described by Romano *et al.* and by Ward on one hand and by Jervell and Lange-Nielsen on the other. The two syndromes, distinguished by the absence and presence of deafness respectively, were considered variants of one disease under the unifying name of long QT syndrome, with the acronym of LQTS.

Molecular studies much later established that genetically and clinically, congenital LQTS is a heterogeneous syndrome. At present, at least 12 variant forms have been formally designated as distinct entities (styled as LQT1 to LQT12). For a more detailed discussion on the complexities of the genetics of LQTS, the reader is referred to other reviews (Vincent, 2000; Priori *et al.*, 2001; Roden, 2006; Schwartz, 2006; Crotti *et al.*, 2008; Zareba and Cygankiewicz, 2008). Although patients with LQTS may experience a range of potentially fatal malignant ventricular tachyarrhythmias including ventricular fibrillation (VF), the prototype arrhythmia most frequently observed in these patients is torsade de pointes (TdP), a polymorphic ventricular tachycardia with a unique morphology on electrocardiogram (ECG). The arrhythmia may result in recurrent syncopes, seizure or sudden death. Depending on the LQTS genotype of the patient, other forms of rhythm disturbances observed include severe sinus bradycardia, paroxysmal atrial fibrillation (AF) and/or 2:1 functional atrioventricular block.

Congenital LQTS was thought to be a rare condition but it is now believed that its prevalence is much higher than previously believed, approaching as much as 1 in 2500. For a further discussion on this, the reader is referred to the review by Crotti *et al.* (2008). More recently, Berge *et al.* (2008) have suggested that although caution is required in interpretation of their findings, the prevalence of heterozygotes for mutations in the LQTS-associated genes in Norway could be in the range from 0.3% to 1%, based on the prevalence of patients with Jervell and Lange-Nielsen syndrome. Because of the low penetration of many mutations, there are clinically silent carriers of long QT mutations (Vincent *et al.*, 1992; Saarinen *et al.*, 1998; Priori *et al.*, 1999). In these individuals, the ECG phenotype is normal and only the molecular genetic studies reveal the concealed subclinical defect in their repolarization reserve. The prevalence of carriers of silent mutations in otherwise healthy individuals is high (Ackerman *et al.*, 2003; Ackerman *et al.*, 2004). Despite a normal ECG phenotype, these individuals are at a greater risk of developing proarrhythmias in response to an appropriate challenge such as therapeutic doses of QT-prolonging drugs that are safe in otherwise normal individuals (Shah, 2004a; Amin *et al.*, 2008; Jeyaraj *et al.*, 2008). Available data suggest that about 10–20% of patients with drug-induced TdP carry silent mutations responsible for congenital LQTS (Yang *et al.*, 2002; Shah, 2004a; Sun *et al.*, 2004; Aerssens and Paulussen, 2005; Lehtonen *et al.*, 2007).

Until 1964, quinidine and thioridazine were the only two widely used drugs known to prolong QTc interval and induce ventricular tachyarrhythmias. With time and increased awareness, a vast number of other non-cardiac drugs have now come to be associated with QT interval prolongation. A brief chronology of drug classes later shown to have the potential to prolong QT interval and induce TdP has been reviewed previously (Shah, 2007). The first entire drug class to be associated with QT liability were the neuroleptic drugs. Indeed, some of these neuroleptics were sufficiently potent in their QT prolonging (class III antiarrhythmic) activity and such was the faith in QT interval prolongation as an efficient antiarrhythmic mechanism that at one time, melperone (a butyrophenone neuroleptic) was being investigated for its use as an antiarrhythmic agent (Mogelvang *et al.*, 1980; Smiseth *et al.*, 1981). The number of torsadogenic drugs has continued to increase inexorably and at present, a large number of drugs from diverse

therapeutic classes have been implicated in prolonging QT interval (de Ponti *et al.*, 2001; 2002; Shah, 2002; 2007). At the last count in April 2009, the author was able to compile a list (unpublished) of just over 160 drugs with clinical and/or strong non-clinical evidence of QT-prolonging effect.

The vast majority of drugs that prolong QT interval in man do so by inhibiting α subunit (encoded by human ether-a-go-go related gene or hERG) of I_{Kr} current that is largely responsible for the duration of cardiac repolarization. Discovery of novel genetic mechanisms underpinning a clinical LQTS phenotype has also provided leads into characterizing drugs for novel mechanisms by which they mimic ('forme fruste') these diseases and induce LQTS. For example, following the discovery of a particular mutation of hERG channel (G601S) (Furutani *et al.*, 1999), it became apparent that congenital LQT2 syndrome could result from deficient cellular trafficking of mutant hERG channel subunits from endoplasmic reticulum to the cell membrane. This discovery was soon to be followed by not only the discovery of other mutations that interfered with trafficking (Robertson and January, 2006) but also by identification of a number of clinically used drugs that induced QT interval prolongation by this novel mechanism (Dennis *et al.*, 2007; Shah and Morganroth, 2008; van der Heyden *et al.*, 2008).

Clinical experience with drugs that prolong QTc interval had also suggested that as with congenital LQTS, the risk of proarrhythmias begins at a QTc interval of about 500 ms and rises exponentially thereafter (Moss, 1999; Shah, 2002; 2004b; Priori *et al.*, 2003). However, a threshold of 500 ms for proarrhythmia is not universal; a number of patients do develop arrhythmias at lower QTc interval values (Vincent, 2003); and prediction of risk still remains difficult. Just as the genetic locus and gender modify the proarrhythmic risk from congenital LQTS (Priori *et al.*, 2003), the risk of proarrhythmia following drug-induced QT interval prolongation is modulated by a number of factors such as ancillary properties of the drug, gender, autonomic influences, co-morbidity and electrolyte imbalance (Shah, 2004b; Pearson and Woosley, 2005; Aström-Lilja *et al.*, 2008). Triangulation of action potential (Shah and Hondeghem, 2005) and an increase in transmural dispersion of repolarization (Antzelevitch and Oliva, 2006) are now believed to be better markers of proarrhythmic risk than QTc interval prolongation per se. Beat-to-beat variability of repolarization is another novel marker for differentiating the extent of torsadogenic potential of drugs that prolong QTc interval (Thomsen *et al.*, 2006; Oosterhoff *et al.*, 2007; Takahara *et al.*, 2008).

Although the risk of TdP following administration of a non-antiarrhythmic drug is sufficiently low that it is unlikely to be detected during clinical trials, mechanism-based concentration-related surrogate markers, APD in *in vitro* studies and QT interval in *in vivo* studies, have long been available by which a new drug could be studied for its proarrhythmic potential during its pre-approval development period. The roles of metabolites and drug interactions as well as stereoselectivity in the interaction between a drug and the ion channels had also become a lot clearer. The regulatory consequence of this improved understanding and an ever-increasing number of QT-prolonging drugs was at first the 'Points to Consider' document adopted by the European Union's Committee for Proprietary Medicinal Products (CPMP, 1997; Shah, 2002) that was later to be superseded by two guidelines (ICH S7B and ICH E14) from the International Conference on Harmonization (ICH, 2005a,b; Shah, 2005).

Thus, in summary, our concerns on drug-induced QT prolongation and its consequences have evolved very gradually. Beginning with description of congenital LQTS that were at first rare enough to be clinical curiosities, we now have stringent regulatory guidance notes requiring all new drugs to be appropriately evaluated for their potential to prolong the QTc interval. This requirement was the outcome of a belated appreciation of the promiscuous susceptibility of ventricular repolarising currents to inhibition by a large number of unrelated drugs and drug classes, resulting in prolongation of QTc interval and induction of potentially fatal ventricular tachyarrhythmias. The regulatory and industry focus on drug-induced QT interval prolongation has also shifted from one of a beneficial antiarrhythmic mechanism to one of a toxic and potentially fatal proarrhythmic property. It has also become evident that there is a striking lack of any correlation between the frequency of congenital LQTS and the number of drugs now known to prolong QTc interval.

Emerging concerns regarding short QT interval and drugs

Congenital short QT syndromes

If a mutation can result in altered function of the ion channel, it should come as no surprise to find that one mutation may result in loss of function whereas another at the same locus may well result in gain of function. For example, in *KCNH2* gene that encodes for the hERG channel, substitution of asparagine by aspartic acid in position 588 (N588D) leads to loss of function whereas substitution of asparagine by lysine in the same position (N588K) leads to gain of function of this channel (McPate *et al.*, 2005).

Gussak *et al.* (2000) were the first to describe an idiopathic short QT interval as a new clinical syndrome in three members of one family. One family member, a 17-year-old girl, required cardioversion for several episodes of paroxysmal AF. At a heart rate of 69 beats·min^{-1}, her QT interval measured 280 ms. Her 21-year-old brother and 51-year-old mother displayed QT intervals of 272 ms (heart rate of 58 beats·min^{-1}) and 260 ms (heart rate of 74 beats·min^{-1}) respectively. Similar ECG changes were also seen in an unrelated 37-year-old patient who experienced sudden cardiac death. Following this seminal observations from Gussak *et al.* (2000), there followed other reports of families with congenital forms of short QT interval associated with arrhythmias and sudden cardiac death (Gaita *et al.*, 2003; Makarov *et al.*, 2004), and it became evident that this syndrome represented a new clinical entity, termed SQTS, with an increased risk for arrhythmias and sudden cardiac death. The general reluctance to accept this finding of great significance is illustrated by the difficulty Gussak *et al.*, (2000) had in having their paper published. Their findings were considered to be due to a flaw in ECG recording technique.

Brugada *et al.* (2004) reported the first gene responsible for SQTS. Genetic investigations of three families with hereditary

Table 1 Parallel between congenital forms of long and short QT syndromes

Channel involved	*Long QT syndrome type*	*Short QT syndrome type*
Potassium channel	Loss of function mutation in *KCNH2* leads to LQT2, *KCNQ1* leads to LQT1, *KCNJ2* leads to LQT7	Gain of function mutation in *KCNH2* leads to SQT1, *KCNQ1* leads to SQT2, *KCNJ2* leads to SQT3
Sodium channel	Gain of function mutation in *SCN5A* leads to LQT3	Loss of function mutation in *SCN5A* leads to Brugada syndrome
Calcium channel	Gain of function mutation in *CACNA1C* leads to LQT8	Loss of function mutation in *CACNA1C* leads to SQT4, *CACNB2b* leads to SQT5

SQTS and a high incidence of ventricular arrhythmias and sudden cardiac death identified two different missense mutations resulting in the same amino acid change (N588K) in *KCNH2*. The mutations dramatically increased I_{Kr} current, leading to heterogeneous abbreviation of APD and reduced the affinity of the hERG channels to I_{Kr} blockers. Subsequently, there followed reports of other variants of SQTS resulting from mutations in genes encoding for other potassium channels (*KCNQ1* and *KCNJ2*) (Bellocq *et al.*, 2004; Priori *et al.*, 2005). Antzelevitch *et al.* (2007) have also described loss-of-function missense mutations in *CACNA1C* and *CACNB2* genes encoding the α_1 and β_{2b} subunits of the L-type calcium channel, giving rise to shorter than normal QTc intervals. On the basis of these molecular studies, at least five distinct forms of SQTS (SQT1–SQT5) are now formally recognized. The correspondence between the genes involved, effect of a mutation on ion channel function and various forms of congenital QT syndromes are summarized in Table 1.

Genotype–phenotype correlations in short QT syndromes

Although the variants of SQTS have been styled as SQT1 to SQT5, the number of patients with these syndromes studied is relatively much smaller than patients studied with LQTS and therefore, the genotype–phenotype correlations of congenital SQTS are at present not as well characterized as they are for congenital LQTS. This is further aggravated by a lack of currently accepted definition of what constitutes a short QT interval (Maury *et al.*, 2005) and the fact that the same mutation resulting in short QT interval may give rise to a range of arrhythmias varying from AF to VF and sudden death (Brugada *et al.*, 2004; Cerrone *et al.*, 2006; Giustetto *et al.*, 2006). Congenital SQTS is associated with high incidence of syncope, sudden death (possibly due to malignant ventricular tachyarrhythmias) or AF, and these events can occur at any age including in infants and the young adolescents (Borggrefe *et al.*, 2005; Hong *et al.*, 2005; Maury *et al.*, 2005; Giustetto *et al.*, 2006).

Normal range of QTc interval

A large number of studies have sought to define the normal range of QTc interval, including variability due to gender, race and age. Because the interval can be influenced by many factors, not least the technique of and equipment for recording the ECG, the ECG leads used for measuring the interval and the formula used for correcting the measured QT interval for heart rate, it is not surprising that there is no universally accepted reference range for QTc interval. Also, almost all the studies have focussed on defining the upper limit of normal QTc interval and there has been hardly any effort until recently towards defining its normal lower limit.

The upper limits of normal QTc interval, corrected for heart rate by Bazett's formula (QTcB), recommended in the first regulatory guidance were 450 ms for adult men and 470 ms for adult women (Moss, 1993; CPMP, 1997). According to Drew *et al.* (2004), a normal QTc interval is <450 ms in men and <460 ms in women. The Report from ACC/AHA/HRS on 'Key Data Elements and Definitions for Electrophysiological Studies and Procedures' defines the upper limit of QTc interval at 440 ms for adult men and 460 ms for adult women (Buxton *et al.*, 2006). From a large dataset of ECGs of 46 129 individuals with a very low probability of cardiovascular disease and using the 2nd and 98th percentiles, Mason *et al.* (2007) have determined normal reference range to be 361–457 ms for QTcB interval and 359–445 ms for Fridericia-corrected QTc (QTcF) interval. On the basis of available data, the present author concludes that 360 ms is probably a reasonable value for the lower limit of normal QTcF interval.

Prevalence of congenital SQTS and silent carriers of mutations

Although a number of studies have investigated the prevalence of congenital LQTS in the population at large, large epidemiological studies investigating the prevalence of congenital SQTS are only a few and these are only recent having been prompted by the description of this syndrome and its potential clinical consequences. Furthermore, the use of different rate-correction formulae has complicated their interpretation. Extramiana *et al.* (2008) have emphasized that correction of measured QT interval by Bazett's formula is not appropriate for making a diagnosis of SQTS. The subject-specific correction formula may provide a better cut-off value for the diagnosis of SQTS. Not surprisingly, therefore, there is at present relatively little experience with, or understanding of the safety implications of, a short QT interval.

Nevertheless, data from Viskin *et al.* (2004) emphasize that QTcB intervals ≤360 ms (for male people) or ≤370 ms (for female people) are not exceptional in healthy adults, especially during bradycardia. The shortest QTc interval observed was 335 ms. Anttonen *et al.* (2007) retrospectively analysed ECGs from 10 822 randomly selected middle-aged men and women with a mean age of 44 years. These investigators corrected the measured QT interval by Bazett and Fridericia corrections as well as by using a nomogram method devised previously by constructing a curve relating QT intervals and heart rates from 40 to 120 beats·min^{-1} (Karjalainen *et al.*, 1994). The prevalence of QTc interval <320 ms, based on QTcB, QTcF or QTcN (nomogram-based correction), was 0.10%, 0.08% or 0.06% respectively, and the corresponding data for QTc interval

values <340 ms were 0.4%, 0.3% or 0.3% respectively. Reinig and Engel (2007) have also reported that SQTS, defined as a QTcB of ≤300 ms, is rare. They were unable to find a single patient with a true QTc of <300 ms in a population >100 000 patients. Similar very low prevalence of QTcB values consistent with SQTS have also been reported in Japanese population (Moriya *et al.*, 2007; Funada *et al.*, 2008). Overall, therefore, these studies suggest that compared with LQTS, ECG-manifest congenital SQTS is probably very rare indeed.

Bezzina *et al.* (2003) reported a significant association between K897T (A2690C), a common *KCNH2* amino acid polymorphism, and QTc interval in German White population. Subjects with CC genotype had significantly shorter QTc interval (388.5 ± 2.9 ms) compared with AA homozygotes (398.5 ± 0.9 ms) and AC heterozygotes (397.2 ± 1.2 ms). The CC genotype frequencies were 5.6% in male people and 5.1% in female people. Itoh *et al.* (2009) have also recently identified another *KCNH2* modifier mutation (R1135H) in a patient with short QT interval (QTc interval of 329 ms). It is not inconceivable that individuals who harbour these mutations may also be at a risk of substantial QT interval shortening when challenged with drugs that normally shorten QT interval only modestly.

Proarrhythmic shortening of QT interval

The link between SQTS and VF has been rendered difficult to interpret because of differences in definition of what constitutes a 'short QT interval'. Because there are other factors that modulate the risk of proarrhythmia, it seems that the expectation of a sharp cut-off value for proarrhythmic shortening of QT interval may be unrealistic if the data on LQTS are anything to go by.

Algra *et al.* (1993) studied the effects of variability in the duration of the QTc interval on the occurrence of sudden death in a nested case–control study. They reported that patients with a prolonged mean QTc interval of >440 ms over 24 h had a 2.3-fold higher risk of dying suddenly than patients with a normal mean QTc (400–440 ms). Perhaps a little surprising at the time was the finding that patients with a shortened mean QTc (<400 ms) also had a higher risk (relative risk 2.4) compared with those who had a mean QTc values in the range 400–440 ms.

Viskin *et al.* (2004) have reported from a case–control study that despite a significant overlap, the QTc interval of male patients with idiopathic VF was shorter than the QTc interval of otherwise healthy male people (371 ± 22 ms vs. 385 ± 19 ms, $P = 0.034$). Short QT intervals were found more frequently among male patients with idiopathic VF (35% vs. 10%, $P = 0.003$). There was a gender effect with no such differences being apparent among women. The authors emphasize that none of the patients had QT interval values as short as those described in the SQTS.

In the study by Gallagher *et al.* (2006), information about subsequent survival was available for 36 of the 60 subjects within the lowest 0.5% of the population studied. None of these subjects died during the 7.9 ± 4.5 years subsequent to the ECG that demonstrated the short QT interval. This apparently reassuring conclusion on the clinical consequences of SQTS should be interpreted with caution as the shortest QTc interval observed was as high as 335 ms and there is no information on the fate of the remaining 24 subjects who could not be traced. However, in the study by Anttonen *et al.* (2007), there were a few individuals with QTc interval <320 ms but all-cause or cardiovascular mortality did not differ between subjects with a short or very short QT interval and those with normal QT intervals (360–450 ms). There were no episodes of sudden cardiac death, aborted sudden cardiac death or documented ventricular tachyarrhythmia among subjects with a QTcF interval <340 ms.

The findings from various studies discussed above are not necessarily conflicting. Whereas the apparently reassuring studies by Gallagher *et al.* (2006), Anttonen *et al.* (2007), Moriya *et al.* (2007) and Funada *et al.* (2008) are observational cohort studies, the ones by Algra *et al.* (1993) and Viskin *et al.* (2004) are case–control studies. Collectively, these studies tend to suggest that the prevalence of SQTS in population at large is very low but the risk of VF in those who have a short QTc interval is much higher than normal.

Alteration in QT/RR relationship is significantly altered in patients with idiopathic ventricular tachycardia (Fei *et al.*, 1994) and idiopathic VF (Fujiki *et al.*, 2004). Another study has also reported that patients with idiopathic VF had shorter QT interval at slower heart rates, a finding suggestive of arrhythmogenicity (Sugao *et al.*, 2006). With regard to SQTS, the QTc interval in most affected subjects is reportedly <300–310 ms without significant dynamic changes during heart rate variation (Borggrefe *et al.*, 2005). A short QT interval is easier to recognize at low heart rates, although with increasing heart rates it tends to be closer to the normal values. Extramiana *et al.* (2008) reported a lower QT rate dependence in patients with SQTS (exponent of 0.146 ± 0.070) when compared with control subjects (exponent of 0.203 ± 0.039, $P < 0.05$).

No doubt, the debate on the proarrhythmic threshold for shortening of QT interval will continue in the immediate future and until the issue resolved, it is the author's view that a Fridericia-corrected value of <320 ms is probably a reasonable one as it seems to correlate better with other electrophysiological substrates of proarrhythmia (Anttonen *et al.*, 2008). As with QT prolongation, proarrhythmic shortening of QT interval is also associated with an increase in transmural dispersion of repolarization, a parameter believed to be a better marker of proarrhythmic risk (Antzelevitch and Oliva, 2006; Anttonen *et al.*, 2008).

Drugs as a cause of QT interval shortening

There is no denying that at present, there is a substantial gap between the existing evidence linking drug-induced QT prolongation to numerous treatment-related fatalities and the less well-documented potential risks and outcomes associated with drug-induced QT shortening. Furthermore, because the prevalence of individuals with SQTS in the population at large is very low, it may be seductive to believe that drug-induced shortening of QT interval need not be such a concern in the development or during clinical use of drugs. However, as with LQTS, there is no scientific reason why there should be any correlation between the prevalence of the two forms – one being congenital depending on frequency of mutations

whereas the other being acquired depending on the number of drugs, which shorten QTc interval. After all, as stated earlier, only 10–20% of patients with drug-induced LQTS carry a pathogenic mutation.

The possibility that clinically used drugs could shorten QT interval had already become apparent when DeSilvey and Moss (1980) reported shortening of QT interval following treatment with primidone in three patients with congenital LQTS. Teh *et al.* (2007) have reported that the mean QTc interval among epilepsy patients was significantly shorter than the QTc interval in the control group. Thirty-five epilepsy patients (50%) and 17 matched controls (24.3%) had a mean QTc shorter than 400 ms. Patients with cryptogenic epilepsy had a mean QTc interval of 392 ± 29 ms, which was significantly shorter than patients with symptomatic epilepsy (QTc = 410 ± 27 ms).

As regards the effect of other anticonvulsants, an ICH E14-compliant 'thorough QT study' has recently reported that lamotrigine induced small reductions in QTcF (maximum mean difference from placebo –7.48 ms; 90% CI –10.49, –4.46) (Dixon *et al.*, 2008). In the broader context, patients with refractory epilepsy face an elevated risk of sudden death, with rates as high as 1% per year (Jehi and Najm, 2008). This phenomenon, known as sudden unexpected death in epilepsy, is believed to be a seizure-related occurrence, but the exact underlying mechanisms are uncertain. Patients with LQTS are frequently diagnosed and treated as suffering from epilepsy (Johnson *et al.*, 2009). Similarly, the possibility that some patients with SQTS experiencing convulsions as a result of a tachyarrhythmia may also be inappropriately diagnosed and treated as having epilepsy should not be dismissed. Notwithstanding, the mechanism of sudden unexpected death in epilepsy also needs to be established (So, 2008) or at least, a proarrhythmic cause needs to be excluded. Based on one well-documented case, Aurlien *et al.* (2009) have also discussed the possibility that one single mutation may explain both the epilepsy and the sudden death observed in epileptic patients. This patient was treated with lamotrigine, and the authors conclude that this drug may also have played a part in inducing a terminal cardiac arrhythmia. During the period from January 1989 to November 2008, the UK regulatory authority (MHRA, Medicines and Healthcare products Regulatory Agency) had received a total of 2530 adverse event reports in association with lamotrigine, of which only two were reports of VF suspected to be associated with this drug (MHRA, 2008). Rufinamide is a new anticonvulsant that has also been found in formal cardiac ECG studies to shorten QT interval (see later for further discussion).

Drugs activating ATP-dependent potassium channel have been known for a long time (Escande *et al.*, 1989). Among the better known are pinacidil, levcromakalim and nicorandil. There is evidence that pinacidil and levcromakalim induce shortening of APD and have profibrillatory effects in preclinical studies (de La Coussaye *et al.*, 1993; Tosaki *et al.*, 1993; Robert *et al.*, 1997; Robert *et al.*, 1999; Extramiana and Antzelevitch, 2004). Nicorandil has frequently been used in the treatment of patients with congenital LQTS (Chinushi *et al.*, 1995; Shimizu and Antzelevitch, 2000). It has complex electrophysiological actions, but its effects are not potent enough to induce any proarrhythmic effect in angina patients with normal QT interval. Mallotoxin and NS1643 (both hERG current stimulators) and levcromakalim and nicorandil (neither having an effect on hERG current) have all been reported to significantly shorten APD and QT interval and elicit VF in isolated hearts (Lu *et al.*, 2008). Nicorandil is already approved for the treatment of angina pectoris. During the period from November 1994 to November 2008, the UK regulatory authority (MHRA) had received a total of 1032 adverse event reports in association with nicorandil, of which six were reports of VF suspected to be associated with nicorandil (MHRA, 2008). However, the author has no information on the QTc intervals in these patients. As a matter of caution, therefore, drugs which are hERG stimulators or are without effect on hERG channel should also be tested for their effect on APD, QT interval and profibrillatory effects.

One of the earliest activators of voltage-gated potassium channel was R-L3, a benzodiazepine, which activates I_{Ks} and was a potential candidate for providing gene-specific therapy for LQT1. Most *KCNQ1* mutant channels, except G306R, responded to R-L3 similarly to wild-type channels (Seebohm *et al.*, 2003). Recently, a number of new drugs have been reported to accelerate I_{Kr} current through an effect on hERG channels (Kang *et al.*, 2005; Zhou *et al.*, 2005; Casis *et al.*, 2006; Hansen *et al.*, 2007; Gordon *et al.*, 2008; Grunnet *et al.*, 2008). In a very extensive programme, Lu *et al.* (2008) measured hERG current in HEK293 cells, APD and arrhythmogenic effects in isolated Purkinje fibres and perfused hearts from rabbits. Of the 576 compounds that were screened in the hERG test, 58% were identified as hERG inhibitors, 39% had no effect, and 3% were classified as stimulators. Of the hERG inhibitors, 92 were tested in the APD assay and of these, 55.4% prolonged APD, 28.3% had no effect, and 16.3% shortened APD. Of the 70 compounds without effect on hERG channels, 54.3% did not affect APD, 25.7% prolonged, while 20% significantly shortened APD.

Just as patients with certain co-morbidities (such as diabetic or Parkinsonian autonomic neuropathy, cirrhosis and human immunodeficiency viraemia) are at a greater risk of QT interval prolongation (Oka *et al.*, 1997; Veglio *et al.*, 2000; Bal and Thuluvath, 2003; Sani and Okeahialam, 2005; Kosar *et al.*, 2007; Lykke *et al.*, 2008), there is preliminary evidence that individual with thyroid disorder or chronic fatigue syndrome have shorter QTc intervals than normal healthy individuals (Asami *et al.*, 2001; Naschitz *et al.*, 2006). Hypercalcaemia and hyperthermia are also risk factors for short QT interval (Saikawa *et al.*, 1988; Curione *et al.*, 2007; van der Linde *et al.*, 2008).

Regulatory perspectives on drug-induced shortening of QT interval

Understandably, progress in addressing any regulatory concern surrounding drug-induced QT shortening has not been as rapid as was the case with drug-induced QT prolongation. Drug-induced TdP resulting from QT interval prolongation is often transient and even if sustained, not uniformly fatal. This effect is therefore often observed in an emergency

room setting. In contrast, VF is uniformly fatal in most cases, and only rarely are such patients resuscitated successfully to link this malignant arrhythmia with short QT interval (Fichet *et al.*, 2008). Consequently, although a short QT interval may be an important cause of VF, evidence linking VF with drug-induced shortening of QT interval may be less easy, if at all possible, to gather than has been the case linking TdP with drug-induced lengthening of QT interval.

In respect of investigating a drug for its QT-prolonging potential, ICH E14 recommends conducting a 'thorough QT study' at supratherapeutic dose and has set a very conservative threshold of regulatory concern. A positive 'thorough QT/QTc study' is one in which the upper bound of the 95% one-sided confidence interval for the largest time-matched mean effect of the drug on the QTc interval includes 10 ms (ICH, 2005b). Analysis of outliers with categorical responses is recommended but is considered to be less sensitive as these studies are not adequately powered for this analysis. Pharmacogenetic evaluation, particularly of subjects with categorical responses, is also encouraged. With regard to investigating a drug for its QT-shortening potential, this is a relatively new and poorly understood potential safety issue and there is hardly any information on the number of drugs that may have this effect, the magnitude of their effects and the clinical significance of the observed effects. In contrast to the known QT-prolonging torsadogenic drugs, there is at present no precedent of a clinically available profibrillatory drug that is known to have a substantial QT shortening effect to provide answers to these important questions. Lack of information is aggravated by an understandable reluctance on part of some sponsors to progress these drugs further into clinical development (Holbrook *et al.*, 2009), arising from uncertainties regarding how regulatory authorities might approach such drugs.

While controlled prolongation of QT interval may have the merit of being antiarrhythmic (e.g. amiodarone), the merit of a short QT interval is not immediately evident. Together with proarrhythmia associated with congenital SQTS, the potential futility of a short QT interval has prompted regulatory authorities to question whether drugs that shorten QT interval could prove to be proarrhythmic. Rufinamide, a triazole-derived anticonvulsant and designated as an orphan drug, illustrates the current pragmatic but cautious regulatory approach to evaluation of drugs that shorten QT interval. Rufinamide is probably the first QT-shortening drug to be approved in the post-ICH E14 days. It is structurally unrelated to currently marketed antiepileptic drugs. It was approved by Committee for Medicinal Products for Human Use in the European Union on 16 January 2007 (EMEA, 2007) and by Food and Drug Administration (FDA) in the USA on 14 November 2008 (FDA, 2008). The maximum therapeutic dose is 3200 mg daily in two divided doses. Rufinamide was found to have no effect on hERG current when investigated in human embryonic kidney cells at concentrations up to 1 $\mu mol \cdot L^{-1}$. Clinically, however, its effect on QTc interval was concentration-related with a decrease of 0.50 ms per 1 $\mu g \cdot mL^{-1}$. This equates to a decrease of 7.5 ms at a typical plasma rufinamide concentration of 15 $\mu g \cdot mL^{-1}$ in patients. At a daily dose of 1200 mg, 1600 and 3600 twice a day in a definitive QT study, rufinamide was found to decrease baseline and placebo-adjusted QTcF interval by a mean of 16.7 ms, 16.1 ms and 20.2 ms, respectively. The concentration-QTcF model revealed the population average maximum QTcF effect of rufinamide to be –27.8 ms (90% CI –30.9, –24.7). In this study a higher percentage of rufinamide-treated subjects (46% at 2400 mg, 46% at 3200 mg and 65% at 4800 mg daily dose) had a QT shortening of greater than 20 ms at peak concentrations compared with placebo rates of 5–10%. However, 92% (at 3200 mg daily dose) to 100% (at 7200 mg daily dose) of subjects recorded a QTc interval decrease of >20 ms during at least one of the time points after dosing. Reductions of the QT interval below 300 ms were not observed in the formal QT studies with doses up to 7200 $mg \cdot day^{-1}$. Moreover, there was no signal of any drug-induced sudden death or ventricular arrhythmias. Although the review of safety data from clinical trials revealed no deaths with a strong potential link to a shortened QT interval and arrhythmias in patients receiving rufinamide, this possibility could not be excluded with confidence in about five cases whose deaths were thought to be related to seizures because, as noted above (Johnson *et al.*, 2009) and in ICH E14 guidance, seizures could occur as a result of a tachyarrhythmia. The FDA-approved label also states, 'The degree of QT shortening induced (by rufinamide) is without any known clinical risk' but goes on warn, 'familial short QT syndrome is associated with an increased risk of sudden death and ventricular arrhythmias, particularly ventricular fibrillation. Such events in this syndrome are believed to occur primarily when the corrected QT interval falls below 300 ms. Nonclinical data also indicate that QT shortening is associated with ventricular fibrillation'. In contrast to the European labelling, the FDA label contraindicates rufinamide in patients with familial SQTS and recommends caution when administering rufinamide with other drugs that shorten QT interval. The European labelling advises use of judgement when prescribing rufinamide to patients at risk from further shortening of their QTc interval (e.g. congenital SQTS or patients with a family history of such a syndrome).

These contraindication and cautions are probably the key to appreciating the regulatory concern and/or caution regarding short QT interval. They are reminiscent of corresponding labels of drugs that induce QT prolongation. Rufinamide is an orphan drug indicated for Lennox–Gastaut syndrome (with a prevalence of 1 per 10 000 of the population), and the prevalence of familial SQTS is sufficiently low (apparently <1 per 100 000 of the population) that the probability of the two conditions coexisting independently in any one patient must be negligible.

If cardiac safety of drugs is a matter of concern, then the non-clinical observations on drug-induced shortening of APD and/or QTc interval and the associated profibrillatory effects discussed earlier should be a matter of concern and should be explored further rather than underestimating their potential significance. Therefore, in the immediate short-term future, the paradigm for assessing the regulatory and clinical significance of drug-induced shortening of QT interval may have to rely increasingly on non-clinical evidence. There is a very obvious role for investigating the effect of QT-shortening drugs on transmural dispersion of repolarization, triangulation of action potential and beat-to-beat variability in repolarization when determining their proarrythmic potential. As

Table 2 Clinically relevant effect sizes for changes in QTc interval

Parameter	*Regulatory thresholds for concern in drug-induced QT interval prolongation (specified in ICH E14)*	*Potential thresholds for concern in drug-induced QT interval shortening#*
Change in central tendency	Mean: +5 ms; 95% upper bound: +10 ms	Mean: −15 ms; 95% lower bound: −30 ms
	Categorical responses of concern	
Absolute QTc interval	≥500 ms	≤320 ms
Change from baseline in an individual	+60 ms	−80 ms

Values stated are QTc interval values corrected for heart rate by subject-specific correction formula.
#This is the current view of the author, and the values proposed are estimates only.

for the clinical data, the paradigm may have to shift from evaluating the effect of a new drug on central tendency of QT interval to evaluating categorical responses, supplemented by pharmacogenetic testing. This is not to suggest that analysis of central tendency in a 'thorough QT study' will not uncover significant shortening of QT interval when the effect is sufficiently substantial. Therefore, if the non-clinical data so warrant, a thorough QT study should be powered and designed to explore this effect as well.

At present, three important issues discussed below warrant addressing when considering whether a drug actually shortens the QTc interval and whether this effect may be a potential harbinger of proarrhythmia. These are: (i) the relationship of the effect to baseline QTc interval; (ii) heart rate correction formula used to compute QTc interval; and (iii) the magnitude of a decrease in QTc interval that may be proarrhythmic.

Whether or not, following a normal QT interval at baseline, a proarrhythmic shortening of the QT interval can be induced clinically by drugs acting at I_{Kr} or other ion channels remains to be seen. Kang *et al*. (2005) have reported that their hERG channel activator (RPR260243) enhanced the delayed rectifier current in guinea pig myocytes. When administered alone, it had little effect on action potential parameters in these cells. However, it completely reversed the action potential-prolonging effects of dofetilide in this preparation. In contrast, however, Zhou *et al*. (2005) reported that their hERG channel activator (PD-118057) was more potent and shortened APD and QT interval in arterially perfused rabbit ventricular wedge preparation in a concentration-dependent manner. Except for rufinamide, much of the current clinical evidence on QT shortening effect of drugs in man has originated from patients with pre-existing prolongation of QTc interval.

As with diagnosing congenital SQTS, Bazett's formula seems inappropriate for making a diagnosis of drug-induced QT interval shortening. In one study, β-blocking drugs typically lengthened QTc interval when corrected by 28 of the 31 formulae and shortened this interval when corrected by the remaining three. However, either effect disappeared when the more rigorous correction formula that provided QTc intervals almost independent of the RR intervals were applied (Malik, 2002). In patients with liver cirrhosis, Zambruni *et al*. (2008) have shown that nadolol shortened QT interval only following the Bazett's correction ($P = 0.01$) but had no effect when the QT interval was corrected by other formulas. Importantly, they also reported that the QT interval shortened only if prolonged at baseline (from 473.3 ± 5.5 to 458.4 ± 6.5 ms; $P = 0.007$), while it lengthened when normal (from 429.8 ± 3.1 to 439.3 ± 2.9 ms; $P = 0.01$). QTc changes were directly related to the baseline value ($P < 0.001$).

Given that the excursion (extent of change from normal point estimate of 430 ms for a normal QTc interval) required for inducing a clinically significant QT shortening (to <320 ms) is larger than that required for QT prolongation (to >500 ms), Table 2 provides the author's estimates of the QT-shortening effect size that may be of clinical relevance. The values pertaining to drug-induced QT shortening in this table are only preliminary estimates to begin the discussion on this important drug-induced effect. These values have been estimated on the assumption that the mean population-based point estimate for a normal QTc interval is 430 ms and the parameters now widely acknowledged as reflecting a QTc-prolonging effect. After allowing for spontaneous variability, a conservative value of 60 ms increase from baseline in QTc interval constitutes another significant categorical response, indicative of a QT-prolonging activity. For a robust evidence of safety, ICH E14 guidance (ICH, 2005b) specifies a mean increase in central tendency of 5 ms with a 95% upper limit of 10 ms. However, for QT interval shortening, the interval has to decrease by a much greater extent to reach a proarrhythmic threshold of 320 ms. After allowing for spontaneous variability, a conservative value of 80 ms decrease from baseline in QTc interval is considered by this author as constituting another appropriate and significant categorical response indicative of a QT-shortening effect in an individual. For an evidence of safety robust enough to convince the regulatory authorities and bearing in mind the greater excursion required, a mean decrease in central tendency of 15 with a 95% lower limit of 30 ms is considered by this author to be approximately equivalent to the threshold identified in ICH E14 guideline for QT interval prolongation.

Conclusions

There is sufficient non-clinical and clinical epidemiological evidence to suggest that shortening of QT interval may be a potential harbinger of proarrhythmia and therefore, a drug effect of safety concern. A serendipitous by-product of compliance with ICH guidelines on drug-induced QT interval prolongation is identification of an ever-increasing number of drugs that shorten APD in repolarization assays and shorten QT interval.

Given the current uncertainty surrounding the clinical significance of a QT-shortening effect and clinically relevant effect size, it may well be that drugs that shorten APD may be approvable subject to a niche indication together with a commitment for heightened a post-marketing surveillance and a safety study to exclude a clinical risk. For example, rufinamide is indicated for adjunctive treatment of seizures associated with Lennox–Gastaut syndrome in children of 4 years and older and adults with, in the USA, a requirement for further analyses aimed at investigating its potential to interact with other QT-shortening drugs. More importantly however, as with QT interval prolongation, there is a need for development of better non-clinical models and a clinical database on which to base informed decisions on the safety and risk/benefit of drugs that shorten APD or QT interval.

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Conflict of interest

None. The author has not received any financial support for writing this review. He was formerly a Senior Clinical Assessor at the Medicines and Healthcare products Regulatory Agency (MHRA), London, UK, and now provides expert consultancy services on cardiac safety of new drugs to a number of pharmaceutical companies.

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