

Editorial

## Drug-induced QT interval shortening: an emerging component in integrated assessment of cardiac safety of drugs

### Introduction

It is nearly a decade since the first description of congenital form of short QT syndrome (SQTS). It is therefore an opportune moment to consider the clinical and regulatory significance of a short QT interval. Before doing so, it may be worth summarizing how our understanding of the clinical and regulatory concerns regarding drug-induced QT interval prolongation and its impact on drug safety has evolved gradually over a period of 40 years.

### Lessons from QT interval prolongation

Congenital prolongation of QT interval (cLQTS) was first described by Jervell and Lange-Nielsen,<sup>1</sup> followed later by a description of another variant of cLQTS by Romano et al<sup>2</sup> and Ward.<sup>3</sup> Although patients with cLQTS 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). At about the time when these 2 variant forms of cLQTS were first described, quinidine and thioridazine were the only 2 widely used drugs known to prolong corrected QT interval (QTc) and induce TdP.

These early reports of cLQTS were later followed by other genetically heterogeneous forms of cLQTS, currently styled as LQT1-LQT12.<sup>4</sup> Concurrently and gradually, there emerged a long list of drugs that replicated the long QT syndrome (LQTS) phenotype (aLQTS), with all the proarrhythmic consequences associated with cLQTS.<sup>5,6</sup> As of February 2010, 13 of the 50 drugs withdrawn from major markets of the world since 1990 were withdrawn because of their QT-prolonging and torsadogenic potentials, with labeling restrictions imposed on countless others. Available evidence suggests that only about 10% to 20% of patients with drug-induced TdP are carriers of the mutations responsible for cLQTS.<sup>7-11</sup>

The regulatory outcome of gradually evolving knowledge on cardiac electrophysiology and clinical consequences of delayed ventricular repolarization, together with an ever-increasing number of QT-prolonging drugs, was the adoption (40 years after the first description of cLQTS) of regulatory guidelines that require sponsors

to investigate all new drugs for their QT-prolonging liability.<sup>5,12-14</sup>

### Congenital QT interval shortening

In 2000, Gussak et al<sup>15</sup> described idiopathic short QT interval as a new clinical entity in 3 members of 1 family. Their QTc ranged from 260 to 280 milliseconds and one of them had required cardioversion for several episodes of paroxysmal atrial fibrillation (AF). Similar electrocardiographic (ECG) changes were also seen in an unrelated 37-year-old patient who experienced sudden cardiac death. After these observations, there followed other reports of families with congenital forms of short QT interval,<sup>16,17</sup> and it became evident that these observations represented a new clinical entity, the SQTS, with an increased risk for arrhythmias and sudden cardiac death. As with cLQTS, it has become evident over the last 10 years that genetically, SQTS is also a heterogeneous syndrome.<sup>18-21</sup>

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. A number of studies have suggested that the prevalence of congenital SQTS is very rare. The genotype-phenotype correlations of congenital SQTS are, at present, not as well characterized as they are for cLQTS, but it is evident that SQTS is associated with AF or potentially fatal ventricular tachyarrhythmias. The reader is referred to an accompanying review by Bjerregaard et al<sup>22</sup> in this issue of the journal.

Although most of the studies correlating the risk of sudden death and/or proarrhythmia with QTc have focused on prolongation of QTc, there are preliminary epidemiological data to suggest an increased risk of sudden death or VF associated with a shortened QT interval.<sup>23,24</sup> In contrast, in 1 large cohort of general population, short QT interval duration was not associated with an increased risk of mortality.<sup>25</sup> However, the number of individuals with short QTc in this cohort was too small ( $n = 7$  with Fridericia-corrected QT interval (QTcF) < 320 milliseconds), and therefore, the study was probably underpowered to give a definitive answer regarding the prognostic significance of a short QT interval. Inevitably, a question arises as to whether drugs are capable of reproducing the clinical phenotype of SQTS with all its clinical implications for cardiac safety of new drugs.

### Preclinical evidence of drugs inducing QT interval shortening

Drugs activating adenosine triphosphate-dependent potassium channel such as pinacidil and levromakalim have long been known to induce shortening of action potential duration (APD) and have profibrillatory effects in preclinical studies.<sup>26-30</sup>

One of the earliest activators of voltage-gated potassium channel was R-L3, a benzodiazepine, which activates slowly activating repolarising potassium current (IKs) and was a potential candidate for providing gene-specific therapy for LQT1.<sup>31</sup> Recently, a number of new drugs have been reported to accelerate rapidly activating repolarising potassium current (IKr) current through an effect on human ether-a-go-go related gene (hERG) channels.<sup>32-36</sup>

Mallotoxin and NS1643 (both hERG current stimulators) have also been reported to significantly shorten APD and QT interval and elicit VF in isolated hearts.<sup>37</sup>

In a very extensive program of investigation of 576 compounds, Lu et al<sup>37</sup> measured hERG current in HEK293 cells, APD, and arrhythmogenic effects in isolated Purkinje fibers and perfused hearts from rabbits. Of these 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, 28.3% had no effect and 16.3% shortened APD. Of the 70 compounds without effect on hERG channels, 25.7% prolonged whereas 20% significantly shortened APD. Of the eight compounds found to be hERG stimulators, three compounds, including NS1643 and mallotoxin, shortened APD.

A recent industry-wide survey (53 total responses representing 45 different companies) indicated that the number of compounds that induce QT/QTc shortening has increased over the past 5 years, with 51% of responses reporting QT/QTc shortening in preclinical studies and 22% reporting a corresponding clinical experience.<sup>38</sup> The reason for the increase is not clear, but there was a clear business impact with 13% (7/56) of these compounds being discontinued in the preclinical phase because of QT/QTc shortening.<sup>38</sup>

### Clinical evidence of drugs inducing QT interval shortening

Among the drugs already on the market, phenytoin and digoxin are believed to shorten QT interval, and both are known to be proarrhythmic. However, the evidence linking either of these drugs to a QT-shortening effect is either absent or only tentative.<sup>39-42</sup> Interestingly, both phenytoin and digoxin have been shown to inhibit hERG channel current,<sup>43,44</sup> and therefore, it would be helpful to study these 2 drugs in the setting of a thorough QT study. Drugs such as nicorandil normalize (as opposed to shorten) QT interval when it is already prolonged.<sup>45</sup> The possibility that clinically used drugs could shorten QT interval had already become apparent when DeSilvey and Moss<sup>46</sup> reported shortening of

QT interval after treatment with primidone in 3 patients with congenital LQTS.

Aurlien et al<sup>47</sup> reported 4 consecutive cases of sudden unexpected death in epilepsy in nonhospitalized patients who were all being treated with lamotrigine monotherapy. All were females with idiopathic epilepsy. In a later study involving DNA analysis in one of these patients, Aurlien et al<sup>48</sup> reported a missense mutation in *SCN5A*, the gene that encodes for cardiac sodium channel. Because this 25-year-old patient was treated with lamotrigine, the authors suggested that this drug may have played a part in inducing a terminal cardiac arrhythmia. The pathogenesis of sudden unexpected death in epilepsy is poorly understood, and without further evidence, one cannot consider lamotrigine as necessarily culpable in these fatalities, but it is interesting that an International Conference on Harmonization (ICH) E14-compliant “thorough QT study” has already reported that lamotrigine induced small reductions in QTcF interval (maximum mean difference from placebo, -7.48 milliseconds; 90% confidence interval, -10.49 to -4.46).<sup>49</sup>

Rufinamide, a triazole-derived anticonvulsant and designated as an orphan drug, is probably the first QT-shortening drug to be approved in the post-ICH E14 period. It is structurally unrelated to currently marketed antiepileptic drugs. It was approved in the European Union in January 2007 and in the United States in November 2008. It was found to be inactive on the hERG channel, but when investigated in formal cardiac ECG studies, it demonstrated significant, concentration-dependent shortening of QT interval (up to 20 milliseconds). In a placebo-controlled study, a higher percentage of rufinamide-treated subjects (46% at 2400 mg, 46% at 3200 mg, and 65% at 4800 mg) had a QT shortening of greater than 20 milliseconds at peak concentrations compared with those treated with placebo (5%-10%). Reductions of the QT interval below 300 milliseconds were not observed even with doses up to 7200 mg/d. Moreover, there appeared to be 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 5 cases in which deaths were thought to be related to seizures. It will be interesting to watch the postmarketing performance of rufinamide, but it is questionable if any useful information will emerge given the rarity of its indication (Lennox-Gastaut syndrome).

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 department 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.<sup>50</sup> 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.

## Regulatory perspective

The Food and Drug Administration–approved label of rufinamide states, “The degree of QT shortening induced (by rufinamide) is without any known clinical risk” but goes on to 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.”

The labeling of rufinamide already signals regulatory unease on the significance of drug-induced QT shortening. The Food and Drug Administration label contraindicates rufinamide in patients with familial SQTS and recommends caution when administering rufinamide with other drugs that shorten QT interval. The European labeling advises use of judgment when prescribing rufinamide to patients at risk from further shortening their QTc duration (eg, congenital SQTS or patients with a family history of such a syndrome). These contraindications and cautions are probably the key to appreciating the emerging regulatory concern regarding the significance of QT shortening. Rufinamide is an orphan drug indicated for Lennox–Gastaut syndrome (with a prevalence of 1/10 000 of the population), and the prevalence of familial SQTS is also low (apparently <1/100 000 of the population)—the probability of the 2 conditions coexisting independently in any one patient must be negligible.

Because cardiac safety of drugs now occupies center stage in the clinical, commercial, and regulatory evaluation of drugs, it is imperative to consider whether drugs can shorten QT interval and adversely influence clinical outcomes. An important reason for apparent indifference to this possibility, advanced by the less cautious in the clinical community, is the reported rarity of congenital SQTS. This reasoning is difficult to understand because drug-induced changes in QT interval are not conditional upon the presence of, or the interaction of the drug with, a genetic substrate.

After the first description of cLQTS in 1957, it was not until 1998 that an editorial called for consideration of exclusion of QT-prolonging properties as a requirement before new molecules were approved for marketing.<sup>51</sup> Available evidence, sparse no doubt it is at present, serves as a caution against dismissing the possibility of drug-induced QT shortening and its consequences. As a matter of caution, therefore, drugs that are hERG stimulators or are without effect on hERG channel should not necessarily be considered safe. They should nevertheless be tested for their effects on APD and QT interval and if the data from these investigations justify, their potential profibrillatory effects. Using escalating concentrations of drugs known to shorten QT interval (levcromakalim, pinacidil, and nicorandil), Kijawornrat et al<sup>52</sup> have described clinically applicable ECG biomarkers for assessment of changes associated with arrhythmogenic risk of VF due to QT interval shortening in sling-trained dogs to evaluate QT-shortening potential of drugs.

As for the clinical QT interval parameters of concern, one of us (R.S.) has previously provided some estimates of

thresholds of concern in the context of a thorough QT study.<sup>53</sup> It is appreciated that at present, there is no evidence base on which to define the proarrhythmic threshold for drug-induced QTc shortening. Therefore, in future, thorough QT studies should also be powered and analyzed to assess the QT-shortening effect of the investigational drug. New drugs that are suspected to induce QTc shortening should be specifically monitored during their postapproval period for their cardiovascular safety generally and proarrhythmic safety specifically.

Rashmi R. Shah, MBBS, MD, FRCP, FPPM

*Rashmi Shah Consultancy Ltd*

*Gerrards Cross, UK*

*E-mail address: [clinical.safety@hotmail.co.uk](mailto:clinical.safety@hotmail.co.uk)*

Preben Bjerregaard, MD, DMSc

*Washington University in St. Louis, USA*

Ihor Gussak, MD, PhD, FACC

*NewCardio, Inc, Princeton, NJ USA*

*Robert Wood Johnson Medical School, USA*

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