Letter to the Editors

QT interval shortening in spontaneous reports submitted to the FDA: the need for consensus

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Drug-induced QT prolongation is recognized as a surrogate marker of cardiotoxicity with significant regulatory and clinical impact [1]. Recently, concern is emerging about the pro-arrhythmic risk associated with QT interval shortening, which is also recognized as a congenital clinical entity that may trigger potentially fatal tachyarrhythmias (i.e. ventricular fibrillation and sudden cardiac death) [2] [w1, w2]. From a regulatory standpoint, whether or not QT shortening (and especially the magnitude of shortening) should be taken as a safety surrogate is a matter of debate [w3, w4], although a recent industry survey estimated that 13% of compounds with QT shortening potential were discontinued in the pre-clinical phase [3].

As compared with drug-induced QT prolongation/torsade de pointes (TdP) [4], the magnitude of the problem in the clinical setting is currently unknown and, to the best of our knowledge, no post-marketing investigations have been carried out. Therefore, we investigated spontaneous reports of QT interval shortening submitted to the FDA Adverse Event Reporting System (FDA_AERS) database.

To this end, publicly accessible quarterly data files (2004–2010) were used (<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm083765.htm>, last accessed 19/04/2011). Methodological issues are detailed in the 'online supporting information' material [w5, w6].

After duplicate removal, 2 131 688 cases were retrieved: QT shortening was reported in 42 cases (as compared with 5323 reports of QT prolongation). Paracetamol was reported in five cases as suspect. Digoxin and ziprasidone received three reports (Table 1). Details on demographic data, concomitant drugs, severity of reports and relevant co-reported adverse drug reactions (ADRs) are provided in the 'online supporting information'.

Notably, in 35 cases (83%), QT shortening was reported in association with arrhythmia-related events, especially with atrial fibrillation (nine reports), some of which were potentially fatal (seven cases with ventricular fibrillation,

Table 1

Synopsis of implicated drugs associated with spontaneous reports of QT shortening

Therapeutic class	Suspect drug*
Antibacterials	moxifloxacin (2), clarithromycin, cotrimoxazole, ceftriaxone, telithromycin
Antipsychotics	aripiprazole (2), clozapine (2), quetiapine, ziprasidone (3)
Antidepressants	imipramine, paroxetine
Anticancer drugs	adalimumab, arsenic trioxide, bevacizumab, capecitabine, dacarbazine, doxorubicin, ifosfamide, melphalan, mesna, natalizumab, sunitinib, thalidomide
Other drugs acting on the nervous system	atomoxetine (2), carbamazepine, chloral hydrate, donepezil, methadone, oxycodone, rufinamide
Anaesthetics	bupivacaine, lidocaine, sufentanyl
Cardiovascular drugs	amlodipine, atenolol, cilostazol, digoxin (3), diltiazem, dobutamine, dronedarone, fosinopril
Antidiabetics	glipizide (2), pioglitazone
Anti-asthmatics	bethametasone, fluticasone, ipratropium, montelukast, salbutamol
Miscellaneous	ascorbic acid, ambroxol, calcitriol, calcium, foscarnet, gadoteridol, gadoversetamide, granulocyte colony stimulating factor, interferon beta-1a, paracetamol (5), phenylephrine, rofecoxib

*number of reports is indicated only if more than one; note that a drug may be reported as PS (primary suspect) or SS (secondary suspect). Please refer to the online supporting information for details.

five with cardiac arrest and three with TdP). QT prolongation and shortening were co-reported in 10 cases.

Most cases occurred in females (62%, three missing data), were serious (i.e. in 68% of cases death, hospitalization or life-threatening events were reported) and submitted by the USA (11 reports, with 14 missing data).

Although the FDA_AERS represents a great opportunity to detect emerging safety issues and increase transparency, several caveats should be addressed before interpreting the results [w7]. In this specific case, the

causality assessment remains challenging due to the high number of reported drugs in each case and lack of additional clinical information (e.g. the actual QT interval value).

As compared with QT prolongation, QT shortening remains elusive. The reasons for this are unclear, but rarity of the event, under-recognition/lack of awareness among physicians and novelty of the topic may play a role. An active monitoring in the next 5 years could provide a more realistic clinical picture, especially if clinicians consider QT shortening among differential diagnoses when suspecting an ADR or a drug-induced arrhythmia. The reporting pattern with serious arrhythmic events is remarkable, consistent with the hypothesis that QT shortening can predict arrhythmia [2] and warrants further investigation (also in terms of risk factors).

For rufinamide and digoxin, reports were expected. Rufinamide is probably the first example of a QT shortening drug approved in the post ICH E14 period, showing a concentration-dependent decrease of the QT interval (7.5 ms at therapeutic plasma concentration, with a maximum effect of 27.8 ms). However, no signals of sudden death or ventricular arrhythmia were detected [5]. The single QT shortening report (out of total 78 ADRs, data not shown) is easily explained by the recent marketing authorization and its restricted therapeutic indication (the Lennox-Gastaut syndrome). Digoxin (three reports) is touted as having QT shortening properties [w8], whereas lamotrigine had no cases retrieved in our analysis, despite a recently documented QT shortening effect [w9].

In several cases, QT shortening was reported with drugs known for QT prolonging effect (e.g. moxifloxacin). While this may be interpreted as an electrocardiographic artifact or even a coding error, one could argue that long and short QT syndrome share similar electrophysiological mechanisms subtending arrhythmogenesis (i.e. increase in transmural dispersion of repolarization with early after depolarizations) [w10, w11]. Because several variables may affect the QT interval, cardiologists should interpret the clinical significance of this electrocardiographic paradox case-by-case. For instance, the imprecision of Bazett's correction may lead to erroneous QT shortening in the case of bradycardia (see reports associated with aripiprazole, atomoxetine and atenolol) [w12].

This exploratory study calls for consensus among regulators and clinicians on event definition (i.e. thresholds of concern in drug-induced QT shortening). On clinical grounds, formal diagnostic criteria have been recently developed [w13]. On regulatory grounds, Shah proposed the following values: 320 ms (absolute value) or an 80 ms decrease vs. baseline (with a mean decrease in central tendency of -15 ms with a 95% lower limit of 30 ms) [5]. Cardiologists should also define 'minimum requirements' to report QT interval abnormalities (e.g. by providing the QT interval value).

In conclusion, drug-induced QT shortening remains elusive and requires further studies on its role as a surrogate marker of pro-arrhythmia. The current interest of the European Union in improving pharmacovigilance calls for multidisciplinary efforts by regulators and clinicians to reach consensus on the definition and reporting of QT interval abnormalities. This will enable pharmacovigilance data to become a more reliable indicator of risk.

Competing interests

There are no competing interests to declare.

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Additional references labelled w1-w13 are available in the Online Supporting Information as 'Web References'.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1

List of spontaneous reports associated with QT shortening, with details on demographic characteristics,

concomitant drugs and co-reported arrhythmia-related events.

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