Drug-induced long-QT syndrome and torsade de pointes: an underrated problem?

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This editorial refers to ‘Epidemiology of symptomatic drug-induced long QT syndrome and torsade de pointes in Germany’ by G. Sarganas et al., on page 101.

Drugs that cause an acquired disorder of myocardial repolarization with a characteristic prolongation of the QT interval on electrocardiogram (ECG) are numerous and widely used for a variety of cardiac and non-cardiac indications. This exposes many patients, who are on these medications, to the risk of a lethal form of polymorphic ventricular tachycardia known as torsades de pointes (TdP). Indeed, one of the most frequent causes of restrictive drug labelling or withdrawal has been prolongation of the QTc interval associated with fatal cardiac arrhythmias. While our increasing understanding of the molecular and cellular changes that are induced by drugs that produce this phenomenon, and our ability to acquire and analyse huge quantities of electrocardiographic data have complemented our clinical observations, it has been noted that the incidence of drug-induced TdP remains difficult to estimate and may, in fact, be much higher than the literature suggests.

In this issue of the Journal, Sarganas et al. have posited that this underestimation of the incidence of drug-induced long-QT syndrome (diLQTS) and TdP may be the result of under-reporting. They attempted to address the problem using active surveillance. In this study, between 2008 and 2011, patients were actively screened at 51 Berlin-area hospitals for diLQTS/TdP using automated QTc measurements. If a patient was deemed eligible, informed consent was obtained and the patient underwent a standardized interview to obtain all relevant information. Importantly, all ECGs were manually re-measured by an experienced ECG reader. Finally, the case was validated by a cardiologist. Information regarding previous and current drug exposure was obtained via interviews with the patients and reviews of the medical charts. Utilizing the World Health Organization (WHO) assessment method, a possible drug aetiology for the case was assigned.

Using the initial screening guidelines, 170 possible cases were referred. After these cases were sorted, based on the inclusion and the exclusion criteria, 58 cases remained. Reasons for dropping cases from the study included inappropriate age, QTc interval below inclusion threshold, the presence of a bundle branch block, the presence of an implantable cardioverter-defibrillator, inability to conduct a patient interview due to discharge or reasons of health, or lack of confirmed symptoms.

The primary finding of this study was that 35 out of the 58 validated cases (60%) were assessed as drug related by applying the aforementioned WHO criteria. The calculated annual crude incidence of diLQTS/TdP was noted to be 3.2 per million person-years, markedly higher than the 0.26 per million rate reported by the German spontaneous reporting system.

We, in fact, may still be underestimating the true incidence since 24 cases could not be validated. Of further concern is that eight cases could not be validated because the patients had died. If these patients had experienced a fatal consequence of drug-induced prolongation of the QT interval, the rate would be 3.7 per million.

This study raises the very important and disturbing possibility that we are missing many patients, who are being exposed to the risk of sudden cardiac death through the use of common medications. While other attempts have tried to simply correlate QTc prolonging drugs with sudden cardiac death, the authors of this study have gone further by specifically demonstrating the presence of QT prolongation in association with these at-risk pharmaceuticals using stringent review of the ECGs.

Another important issue raised by this study is that 19 out of the 42 drugs listed as related to LQTS/TdP are not found on the list of medications commonly thought to cause QT interval prolongation. Thus, we may be significantly underestimating the number of at-risk medications, and begs the question of whether more stringent testing for these effects ought to be considered prior to final approval of new chemical entities.

Confounding the picture is the presence of many independent risk factors for QT prolongation that may not be quantifiable. This study found that with the 19 drugs not included in the list of common QT prolonging medications, there were a total of 27 reactions. As this
study points out, in many of these reactions another cause could not be excluded. One of the more common risk factors in the diLQTS/ TdP cases was, in fact, hypokalaemia, occurring in 60% of cases in which a potassium level was measured.\textsuperscript{7}

A possible genetic predisposition to LQTS was also alluded to. For example, the human ether-a-go-go-related gene (HERG), which encodes the subunits of the \(I_{\text{kr}}\) potassium channel of the heart, is known not only to have mutations that cause type 2 long-QT syndrome, but is also the most common target for drugs that cause diLQTS.\textsuperscript{7} Furthermore, it has been suggested that there might be a ‘repolarization reserve’ made possible by a redundancy in repolarization currents that may allow mutations to remain clinically silent.\textsuperscript{8}

With the addition of yet another insult, such as electrolyte derangements, structural heart disease, or concomitant medications, the effects of the mutation becomes manifest.\textsuperscript{9}

Having established the significance of the problem as well as its complexity, the obvious question is where do we go from here? Further studies in incidence and prevalence of diLQTS/TdP should be undertaken, albeit in larger and more varied populations. The expanding use of electronic medical records, and the large and more easily accessible data they provide, should be exploited to help facilitate this.

Taking a more proactive approach, the use of pre-clinical models may help remedy some of the inadequacies encountered above. Of particular interest may be the use of human cardiomyocytes created from embryonic stem cells and induced pluripotent stem cells. \textit{In vitro} studies using this model have demonstrated its potential utility in pre-clinical screening of drugs for their effects on myocyte action potentials prior to actual clinical drug exposure.\textsuperscript{10} Specifically, Liang et al.\textsuperscript{11} demonstrated how a library of human-induced pluripotent stem cell-derived cardiomyocytes from patients with a variety of hereditary cardiac disorders demonstrated different susceptibilities to action potential prolongation. This represents a powerful prognostic tool and may help guide future identification of risky drugs that otherwise would have remained unidentified.

In summary, we have identified a complex problem that is potentially more widespread than previously thought, with devastating consequences for patients and their families. The fundamental principle of medicine is to do no harm and yet the very medications we prescribe to help our patients with a myriad of diseases may be placing them at risk for sudden death. Much work has yet to be done to fine tune our knowledge to allow us to prescribe medications that maximize the benefits to our patients while minimizing their risks.

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\textbf{References}