What Causes Some Patients with Drug-Induced QT Interval Prolongation to Develop Torsades de Pointes but Not Others? The Elusive Missing Link

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Cardiac arrest due to torsades de pointes (TdP) is an uncommon but potentially catastrophic event associated with QT interval-prolonging drugs [1]. Numerous medications that may cause TdP are available for use in clinical practice, and include drugs for management of cardiovascular diseases, primarily arrhythmias, but also noncardiovascular agents from multiple classes, including anti-infectives, antipsychotics, antidepressants, methadone, and many more [2]. The risk of TdP increases as the heart rate-corrected QT (QT_c) interval increases [3–6], particularly when it exceeds 500 ms [5, 6]. Numerous independent risk factors for QT_c interval prolongation and TdP have been identified, and include female sex, hypokalemia, hypomagnesemia, acute myocardial infarction, sepsis, supra-therapeutic concentrations of QT_c interval-prolonging drugs, rapid intravenous infusion of QT_c interval-prolonging drugs, concomitant administration of two or more QT_c interval-prolonging drugs, concomitant administration of a loop diuretic, bradycardia, heart failure with reduced ejection fraction (HFrEF), pretreatment QT_c interval prolongation, and ion channel polymorphisms [7, 8].

Some evidence indicates that older age is also a risk factor for prolonged QT_c interval [8–10] and TdP [11]. In

the Third National Health and Nutrition Examination Survey (NHANES III), age was associated with prolonged QT_c interval in men [8]. In a study of hospitalized patients, age >60 years was reported to be a risk factor for drug-induced QT interval prolongation [9]. In another study of hospitalized patients, age ≥68 years was shown to be an independent risk factor for QT_c interval prolongation in patients in cardiac care units [10]. Age ≥65 years is an independent risk factor for TdP associated with azimilide [11]. Mechanisms underlying an increased risk of drug-induced QT_c interval prolongation and TdP in older patients are unclear, but could include declining serum testosterone concentrations in older men [12, 13] and reduced serum progesterone concentrations in postmenopausal women [14]. QT_c interval-prolonging medications are prescribed commonly to older patients [15]; therefore, awareness of the degree of risk and strategies for mitigating the risk of QT_c interval prolongation and TdP in this population are desirable. Although it is known that the risk of TdP increases as the QT_c interval increases, there is a missing link; only a small portion of patients that develop drug-induced QT_c interval prolongation experience TdP. It is unknown why some patients with drug-induced QT_c interval prolongation experience TdP and some do not, and whether there are risk factors that predispose patients with drug-induced QT interval prolongation to develop TdP. Information that could shed light on this mystery would advance the field and contribute important knowledge regarding mitigation of TdP risk.

In this issue of *Drugs and Aging* [16], Goutelle and colleagues attempt to identify factors that predispose elderly patients with drug-associated long QT_c interval to development of TdP. In this retrospective, case–control study, the investigators queried the national French pharmacovigilance database for cases of long QT_c interval and

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TdP occurring in patients ≥ 65 years of age during the years 2000–2009. The cases were divided into two groups: (1) patients who developed drug-induced long QT_c interval (defined as QT or QT_c interval >450 ms) and also experienced TdP ($n = 125$), and (2) patients who developed drug-induced long QT_c interval but did not develop TdP ($n = 81$). Drugs that were most commonly associated with QT_c interval prolongation and/or TdP included amiodarone, furosemide, digitalis drugs, and sotalol, among others. Univariate comparison of the two groups demonstrated significantly higher odds ratios for TdP associated with uncorrected (but not corrected) QT interval, digitalis drugs, and a mixed group of other potential drug culprits. However, multivariate regression analysis revealed only one independent risk factor for TdP, which was uncorrected QT interval (odds ratio 1.013, 95 % confidence interval 1.004–1.022, $p = 0.0014$).

Limitations of this study acknowledged by the investigators include its retrospective case–control design, although in fairness, a prospective, randomized, controlled study to determine risk factors that predispose patients to TdP would not be feasible. Nonetheless, the study design is subject to the biases inherent in retrospective studies of spontaneous reporting databases, including potential underreporting of events, notoriety bias, and variable data quality and integrity. Other limitations include the fact that the investigators relied upon QT interval measurements reported in the database, and there was not an opportunity to verify the accuracy of QT interval measurements using a consistent method of assessment. Because of the nature of the data, patients with QRS duration >120 ms, including those with left bundle branch blocks and functioning ventricular pacemakers, were not excluded; this can affect the accuracy of the QT interval measurements, and it is unknown whether the distribution of such patients varied between the two study groups. The method for the heart rate correction of the QT intervals was not available in the majority of the reports. The definition of drug-induced long QT interval syndrome used in the study was QT_c >450 ms. However, the upper limits of normal for QT_c interval in men and women are 470 and 480 ms, respectively [1]. In addition, the majority of data have identified a QT_c interval >500 ms as the point at which the risk of TdP increases markedly [5–7]; this may be a more appropriate definition of drug-induced long QT interval syndrome.

Despite these limitations, there is merit in the analysis of Goutelle and colleagues [16], as it remains unknown whether there are specific factors that predispose patient with prolonged QT_c interval to develop TdP, and whether there are identifiable differences between patients with prolonged QT_c interval that develop TdP and those who do not. The results of their analysis are surprising, in that widely accepted risk factors for TdP including female sex,

hypokalemia, and heart disease (including HFrEF) did not emerge as independent risk factors for TdP. This could be due to some or all of the aforementioned limitations of the study. Alternatively, it is possible that female sex, hypokalemia, heart disease and other risk factors contribute to lengthening of the QT_c interval, but do not contribute additionally to the occurrence of TdP once the QT_c interval is already prolonged. As this analysis was confined to patients ≥ 65 years of age, it is also possible that the influence of some or all of these risk factors is lessened in older patients. These questions require further investigation.

Goutelle and colleagues [16] reported that uncorrected QT interval (but not the corrected QT interval) was the only independent predictor of TdP in this study. This could again be attributed to the aforementioned study limitations pertaining to QT interval measurements and/or correction, inclusion of patients with prolonged QRS duration, and/or definition of QT_c interval prolongation. However, this finding is consistent with some previous data. In a study of critically ill patients who received intravenous haloperidol ($n = 46$) for delusional agitation, of whom $n = 7$ developed TdP, uncorrected QT interval was a significantly better predictor of haloperidol-associated TdP than Bazett's or Fridericia-corrected QT interval [17]. Framingham-corrected QT interval offered no advantage over QT intervals not corrected for heart rate. Uncorrected QT interval measurements have been shown to be more reliable than Bazett's or Fridericia-corrected QT intervals [18]. In addition, heart rate correction of QT intervals is often performed inaccurately, even by physicians and cardiologists [19]. Use of uncorrected rather than heart rate-corrected QT intervals may offer advantages of simplicity and accuracy; further study is required to determine whether uncorrected QT interval can reliably replace heart rate-corrected QT interval for assessment of risk of TdP.

Goutelle and colleagues [16] attempted to identify factors that predispose elderly patients with drug-induced long QT interval syndrome to develop TdP. While their effort is important, the paucity of factors identified in their study leaves open questions that require further scientific inquiry, including the following: (1) Why do some patients with drug-induced long QT interval develop TdP while others do not? (2) Are there as yet unidentified risk factors that predispose patients with drug-induced prolonged QT interval to develop TdP? (3) Does the influence of specific risk factors for TdP such as female sex, electrolyte abnormalities, heart disease, and others change or diminish with advancing age? As long as these and other important questions remain unanswered, the missing link remains elusive.

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