

## EDITORIAL

# Drug-Induced QT Prolongation: An Update

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Ventricular repolarization duration as measured on the surface electrocardiogram by the QT interval and the heart rate corrected QT interval (QTc) may be influenced by many factors. In normal healthy subjects, the normal range of the QTc interval is quite broad ranging from 0.38 to 0.45 seconds, with age and gender modifying the range.<sup>1</sup> Furthermore, in any given subject, the QTc interval can be variable from one day to the next, even when taken at the same time of the day and at the same heart rate. In addition, the formulae for correction of the QT interval for heart rate are problematic, especially at heart rates <50 and >90 bpm. As information has accumulated during the past decade from studies involving the hereditary long QT syndrome, we now have a better understanding of genetic factors that account for the normal variance in the QTc duration. Presently, seven ion-channel related genes have been identified, and genetic variations within these genes can profoundly influence the balance of ion-channel currents that determine the duration of the myocyte's action potential, and thus the QT interval as recorded on the electrocardiogram. Of course, the factors influencing the QT interval at any given instant are complex for they include genes and gene products that can modify the function of specific ion channels, autonomic nervous system activity, cellular calcium channel dynamics, temperature, heart rate, and various acquired factors such as diseases and drugs.

It had been known for 50 years or more that certain drugs could prolong the electrocardiographic QT interval. Quinidine was notorious in this regard, especially when used to convert atrial fibrillation to sinus rhythm in patients with rheumatic heart disease. Quinidine syncope and quinidine-related sudden cardiac death were well-recognized clinical entities, and careful monitoring of the QT

interval was recommended during loading and maintenance therapy with quinidine. A few well-documented cases linked quinidine therapy to transient polymorphic ventricular tachycardia as the cause of syncope and to ventricular fibrillation as the basis for sudden cardiac death. It was also appreciated that other antiarrhythmic drugs had QT prolonging properties, but this risk was considered acceptable until the cardiac arrhythmia suppression trial (CAST) showed that promising antiarrhythmic drugs were associated with a higher mortality than placebo therapy.<sup>2</sup>

The situation advanced dramatically in the early 1990s when the blockbuster antihistamine drug, terfenadine (Seldane), was found to be associated with unexpected sudden cardiac death in a small number of overly healthy individuals taking this medication.<sup>3</sup> Through good medical detective work, it was recognized that terfenadine alone could have a modest QT prolonging effect, but when taken together with certain antifungal agents that inhibit the hepatic metabolism of terfenadine, toxic levels of terfenadine could develop with marked QT prolongation and an increased probability for life-threatening ventricular tachyarrhythmias. Within a few years of these findings, terfenadine was removed from the marketplace and replaced with its metabolite, fexofenadine (Allegra), a drug with good antihistamine properties but no QT prolonging effects.

The terfenadine story prompted the U.S. Food and Drug Administration to more carefully scrutinize all new drug applications for drug-related QT prolongation. These concerns prompted various drug-regulatory agencies throughout the world to become involved in the expanding drug-related QT-prolongation problem. Various guidelines were established for drug testing,<sup>4</sup> and it was soon

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appreciated that a wide spectrum of exiting and approved drugs including antibiotic and antipsychotic medications had QT prolonging effects that could cause dangerous arrhythmias under the proper conditions. A second blockbuster drug, cisapride (Propulsid), a prokinetic gastrointestinal drug was removed from the market in July 2000 because of its QT prolonging effects and 80-associated sudden deaths.<sup>5</sup>

In 2005, the U.S. Food and Drug Administration upgraded its requirements for QT prolongation drug testing.<sup>6</sup> Because of the recognized difficulty in accurately and reproducibly measuring the QT interval, the agency required that new drug testing should include a comparator drug, an approved drug with mild yet benign QT prolongation, to be sure that the QT measurement was being accurately performed. The U.S. agency indicated that the approved antibiotic, moxifloxacin, was an acceptable comparator for it produced, on average, a 6 ms prolongation in the QT duration.

This issue of *Annals* includes an evaluation of the effects of three approved fluoroquinolones (ciprofloxacin, levofloxacin, and moxifloxacin) on the QT interval and QT dispersion. Moxifloxacin was the only fluoroquinolone with QT prolonging effects—approximately 12 ms lengthening of the QT interval after 7 days of maintenance therapy. Of note, none of the three fluoroquinolones had any measurable effect on QT dispersion. These findings indicate that fluoroquinolones as a class do not have QT prolonging effects. Clearly, the effect is influenced by the specific chemical structure of the drug (moxifloxacin). In this regard, it is interesting that recent studies indicate that virtually all the QT prolonging drugs exert their effect through physical-chemical binding of the drug to the pore compo-

nent of the HERG ion channel, with reduction in the rapidly activating potassium repolarizing current,  $I_{Kr}$ .<sup>7</sup> Reduction in the  $I_{Kr}$  current occurs with mutations involving the pore region of the HERG ion-channel protein (LQT2 form of the long QT syndrome)<sup>8</sup> and with drugs that adversely influence the movement of potassium ions through the pore region of the channel. Insight into the fundamental mechanism responsible for drug-induced QT prolongation has been enhanced by our understanding of the genetic and molecular basis of ventricular repolarization.

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