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EDITORIAL COMMENT

Should We Use Drugs to Decrease Drug-Induced QT Prolongation?*

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The QT interval prolongation predisposes to the development of torsades de pointes (TdP) ventricular tachycardia and ventricular fibrillation, which could lead to syncope, cardiac arrest, or sudden cardiac death (1-5). Drug-induced QT prolongation and TdP has been recognized as a side effect of many commonly used medications. The association between a specific drug and development of TdP is difficult to document; therefore, QT prolongation is considered a surrogate marker of the proarrhythmia risk. Frequently prescribed drugs such as azithromycin, erythromycin, or antipsychotic drugs block the I_{Kr} current, but they rarely cause life-threatening arrhythmias (5). Susceptibility to drug-induced QT prolongation and TdP is multifactorial, and a combination of several factors is needed for arrhythmias to occur, including female sex, advanced age, electrolyte abnormalities, comorbidities, and concomitant medications acting on ion channels or drug metabolism. Female sex is one of the most important factors because even healthy females show a longer QTc than males. Women account for 70% of cases of drug-induced QT prolongation and TdP, indicating that sex-related differences in repolarization duration might predispose women to proarrhythmias (5).

Patients with congenital long QT syndrome (LQTS) show the same pattern, especially in the case of LQT1 caused by the KCNQ1 gene mutations affecting the delayed rectifier current (I_{Ks}) current and LQT2 caused by HERG gene mutations affecting the I_{Kr} current. In both of these forms of the LQTS, females have higher event rates than males after puberty (1-4); the reasons for these differences are still not well-understood because the risk is increased after adjustment for covariates including QTc duration and heart rate. The observation that females continue to have an increased risk after puberty, but the risk for males levels off after puberty indicates that differences in hormonal status might play a role in females' predisposition to longer QTc and to cardiac events (2-4). Our data demonstrate that women with LQTS have a low risk of cardiac events in pregnancy when progesterone levels are elevated, whereas their risk increases in the postpartum period when progesterone levels decrease (6). This observation indicates a possible protective effect of progesterone.

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In this issue of *JACC: Clinical Electrophysiology*, Tisdale et al. (7) present the results of an interesting study evaluating effects of oral progesterone administration on drug-induced QT interval prolongation. They conducted an elegant double-blind crossover study in 15 healthy females who were randomized to receive progesterone 400 mg or matching placebo for 7 days. On day 7, ibutilide was infused to induce QT prolongation. Serum progesterone concentrations were measured during the progesterone phase as proof of drug administration. They used QTcI, an individualized correction for assessing changes in QT with heart rate. The QtcI increased significantly less in response to ibutilide during progesterone treatment than in the placebo phase (443 ± 17 ms vs. 458 ± 19 ms; $p = 0.003$). These observations document that oral progesterone administration decreases drug-induced QT prolongation.

This is the first study demonstrating oral progesterone administration shortening drug-induced QT

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prolongation. The mechanisms behind this action are not known; however there are a few concepts that can be considered. Progesterone enhances the slow component of I_{Ks} and inhibits L-type Ca 2^{+} current under cyclic adenosine monophosphate-stimulated conditions mediated by nitric oxide release (8). Progesterone binding to σ-receptors blocks σ-receptor-mediated modulation of a voltage-gated sodium ion current (I_{Na}), and this novel membrane action of progesterone may be relevant to the QT-shortening effect of the drug (9).

Ranolazine, a late sodium current blocker, was shown to reduce drug-induced TdP in the chronic atrioventricular block dog model (10). Eleclazine, a novel selective late I_{Na} current blocker was associated with significant shortening of the dofetilide-induced QTc prolongation in healthy subjects (11). LQT3 patients, with mutations causing impairment of late I_{Na}, show significant QTc shortening in response to eleclazine (12). Because there is a growing evidence for the QTc shortening effect of late I_{Na} current blockers, it is plausible that the mechanisms of progesterone shortening QT could be mediated by sodium current, as suggested by Johannessen et al. (9). In future investigations, it will be interesting to evaluate JT peak and T_{peak} - T_{end} intervals in the studied women to further explore potential ion channel effects along with recent work indicating that these variables might provide insight into a multichannel action of the drugs (13). They also could investigate changes in T-wave morphology to further understand the effects that might be mediated by the I_{Kr} currents (14). The overall concept of decreasing QT in life-threatening TdP situations by medications is very attractive, and the study of Tisdale et al. (7) paves the way toward further clinical explorations toward effective use of measures reducing the risk of drug-induced side effects.

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