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The funny and not-so-funny effects of dronedarone

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Atrial fibrillation (AF) is the most common supraventricular tachycardia, affecting over 2 million patients, and is associated with 100,000 new strokes per year.¹ Data from large, long-term epidemiologic studies such as the Framingham Heart Study show a strong link between AF, stroke, congestive heart failure, and mortality.² In addition, the expected rise in the elderly population in Western countries will cause an increase in the clinical burden of AF.³ Historically, AF has been treated by pharmacological rate and/or rhythm control in combination with chronic oral anticoagulation medication to reduce the risk of embolic phenomena. Large-scale randomized control trials have shown that rhythm control with antiarrhythmic drugs is not superior to a strategy of rate control, most likely owing to the proarrhythmic risk and poor efficacy of contemporary antiarrhythmic drugs.⁴ These findings have increased the need for better pharmacological approaches for the treatment of AF.

Current pharmacological options for the management of AF span all Vaughn-Williams classes of antiarrhythmic drugs. For patients who tolerate AF, rate control is typically achieved with beta-blockers (class II) and calcium channel blockers (class IV). Symptomatic patients with AF routinely require the addition of sodium channel blockers (class I) or potassium channel blockers (class III) to achieve rhythm control. The proarrhythmic risk profile of class I and class III agents has largely limited their use in patients with structural heart disease or baseline QT interval prolongation. Of these agents, amiodarone has consistently been the most effective in maintaining sinus rhythm.^{5,6} However, the risks of long-term amiodarone use are substantial and include numerous drug-drug interactions and end-organ damage, particularly pulmonary, hepatic, and thyroid toxicity. The need for more effective rhythm control agents with improved safety profiles led to the development of dronedarone.

Dronedarone is a class III antiarrhythmic drug that was recently approved as an alternative to amiodarone for the treatment of AF and atrial flutter. Structural modifications to dronedarone, including the lack of an iodine moiety and the addition of a methanesulfonyl group, were hypothesized to decrease the thyroid and pulmonary toxicities associated with amiodarone.⁷ The antiarrhythmic mechanisms of action remain largely unclear. Similar to amiodarone, dronedarone is a multichannel blocker that affects several outward currents including the rapid (I_{Kr}) and slow (I_{Ks}) components of the delayed rectifier and the

acetylcholine sensitive potassium currents (I_{ACh}) and may also reduce the inward currents including the sodium (I_{Na}) and L-type calcium currents (I_{CaL}). Initial studies demonstrated the superiority of dronedarone over placebo in the maintenance of sinus rhythm in patients with paroxysmal and persistent AF or atrial flutter.⁸⁻¹⁰ As a rate control agent, dronedarone has been shown to reduce the mean 24-hour ventricular rate response during recurrent or permanent AF, and the ventricular rate response during peak exercise.^{8,10,11} The mechanisms responsible for the reduction in ventricular rate remain unclear. However, recent data indicating dronedarone suppresses pacemaker currents including the funny current (I_f) in the sinoatrial node have emerged. I_f is an inward current that is found throughout the specialized conduction system and contributes to atrioventricular (AV) nodal conduction. Determining whether dronedarone has similar effects on I_f in the AV node could provide important information on the mechanisms responsible for heart rate slowing during AF.

In this issue of *HeartRhythm*, Verrier et al¹² provide a series of new and interesting experiments exploring the effects of dronedarone on baseline electrophysiological parameters and ventricular rates during AF by using a porcine model. The authors studied intact anesthetized animals and induced AF with a combination of acetylcholine infusion and burst pacing. Consistent with the known effects of dronedarone, at baseline the drug increased PR and QT intervals as well as atrial and ventricular refractory periods. The authors then performed a series of studies comparing the effects of the I_f blocker, ivabradine alone, and a combination of ivabradine and dronedarone on ventricular rates during induced AF. Both drugs were shown to have no effect on mean arterial pressure, AF duration, or AF dominant frequencies. The authors reported that ivabradine significantly reduces ventricular rates during AF than do ventricular rates obtained during AF at baseline. These data support the interesting concept that blocking AV nodal I_f slows AV conduction, resulting in lower ventricular rates during AF. The authors then tested whether a combination of ivabradine and dronedarone would cause any additional reduction in ventricular rates during AF. The data obtained during the combined ivabradine and dronedarone administration were not significantly different compared with the ivabradine-alone studies. Since the authors did not find either drug-affected AF dynamics, the reduction of ventricular rate appears to be due to slowing of conduction within the AV node. Although indirect, these data for the first time implicate AV nodal I_f as an important mechanism in mediating the heart rate slowing effects of dronedarone during AF.

In addition to the limitations mentioned by the authors, there are a few additional comments that are worth considering. Although ivabradine has potent I_f blocking properties, it should be noted that it is not a pure I_f blocker. Studies have shown that ivabradine can partially block the delayed rectified and L-type calcium currents. These effects tend to be more prominent at concentrations higher than those used by Verrier et al.¹² Thus, the potential involvement of other AV nodal ionic currents in reducing ventricular rates during AF should not be excluded. The authors also did not report the effects of dronedarone or ivabradine on AV nodal electrophysiological parameters such as Wenckebach cycle length, A-H intervals, and AV nodal effective refractory periods. These data could have added information implicating AV nodal conduction and possibly I_f more directly. Finally, as the authors

indicated in their Introduction, it should be emphasized that several studies have demonstrated that dronedarone is not suitable for all patients with AF. The ANDROMEDA trial demonstrated increased mortality with the use of dronedarone in patients with AF and significant heart failure.¹³ Furthermore, the results of the PALLAS study, which evaluated dronedarone as a rate control agent in high-risk patients with permanent AF, showed increased cardiovascular events in the dronedarone arm.¹⁴ These results prompted the Food and Drug Administration to issue a black box warning that dronedarone is contraindicated in patients with New York Heart Association class IV heart failure or New York Heart Association class II–III heart failure with recent decompensation requiring hospitalization and in patients with permanent AF. Finally, an intriguing finding of the Verrier et al¹² study is that the heart rate slowing properties of ivabradine during AF is substantial and may be equivalent to dronedarone. Recent studies have suggested that the suppression of I_f in the pulmonary veins can suppress atrial ectopic activity and possibly AF. Given the additional evidence provided by Verrier et al¹² that I_f blockade also significantly reduces ventricular rates during AF, it may be worth considering whether I_f blocking drugs may be effective for both rate and rhythm control. Overall, Verrier et al¹² should be congratulated for their excellent study and for adding important new information on the antiarrhythmic properties of dronedarone.

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