News and Views From the Literature

Antiarrhythmic Drugs

Combination Ranolazine and Dronedarone to Suppress Atrial Fibrillation

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Synergistic Effect of the Combination of Ranolazine and Dronedarone to Suppress Atrial Fibrillation

Burashnikov A, Sicouri S, DiDiego JM, et al.

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Atrial fibrillation (AF), which affects approximately 2 million people in the United States, is the most common arrhythmia requiring medical intervention. It is a major cause of stroke, adversely impacts quality of life, and is associated with increased mortality. Despite a variety of treatment options, including pharmacotherapy and device-based therapy, we do not have effective therapies for suppressing AF, particularly the persistent and chronic varieties. Antiarrhythmic drug therapy remains the first and most appropriate therapy in most patients to convert and maintain normal sinus rhythm. Currently available antiarrhythmic drugs are limited by modest efficacy and significant toxicity. Cardiac toxicity relates to effects on the ventricle, especially in prolonging the QT interval and causing torsades de pointes. In one trial, only 39% of patients randomized to the antiarrhythmic drug group were in sinus rhythm at the end of the study.[1] Ablative procedures have short-term cure rates of up to 70% when performed in good candidates, such as younger patients with paroxysmal AF and normal left atrial dimension. Ablation was associated with elimination of symptomatic atrial arrhythmia in 70% of patients with symptomatic paroxysmal atrial arrhythmias, and elimination of any atrial arrhythmia irrespective of symptoms in 63% of patients at 1 year.[2] The long-term success of a single ablative procedure leads to long-term (5-year) arrhythmia-free results in approximately 29% of treated patients.[3] However, ablative procedures are much less likely to be effective in patients with more persistent and chronic AF and in association with underlying structural defects such as left atrial enlargement and mitral valve and left ventricular (LV) dysfunction.

Burashnikov and colleagues present their findings on the synergistic effect of the combination of ranolazine and dronedarone on suppressing the recurrence of AF in a dog model. Dronedarone is a noniodinated derivative of amiodarone with a superior safety profile when compared with amiodarone, but is less efficacious. There have been two reports of severe hepatotoxicity with dronedarone use. It displays a wide cellular electrophysiological spectrum largely similar to amiodarone, inhibiting the potassium

currents I_{Kr}, I_{Ks}, I_{KI}, I_{KACh}, and I_{sus}, as well as sodium currents and L-type calcium currents in isolated cardiomyocytes. Ranolazine is an antianginal agent, which inhibits normal and abnormal late Na+ channel current in the ventricle and peak Na+ channel current in the atrium. By this inhibition, it affects intracellular calcium handling producing an energy-sparing effect. Ranolazine has also been shown to be a potent inhibitor of afterdepolarizations produced by a number of mechanisms that may impart its antiarrhythmic effects. The anti-AF efficacy of ranolazine is thought to be related to the atrial selective inhibition of early sodium current (I_{Na}).

This study was spurred by previous findings that the addition of ranolazine to chronic amiodarone therapy led to depression of atrial-dependent I_{Na}, which was believed to be the mechanism for the effective suppression of AF that was observed in canine isolated atria. The combination was found to suppress delayed afterdepolarization- and early afterdepolarization-induced triggered activity in the pulmonary veins—the site of AF initiation. The studies of Burashnikov and colleagues were performed using isolated coronary-perfused canine right atrial (RA) and LV preparations. Ranolazine, 5 μmol/L, and dronedarone, 10 μmol/L, combined did not result in significant prolongation of the action potential duration in either the RA or LV preparations. Persistent AF was induced in these preparations in the presence of acetylcholine (1 μmol/L). When administered separately, dronedarone and ranolazine were not effective in preventing the induction of AF. However, when combined, dronedarone and ranolazine were 90% effective in preventing the induction of AF (Figure 1). This study is a "proof of concept" that

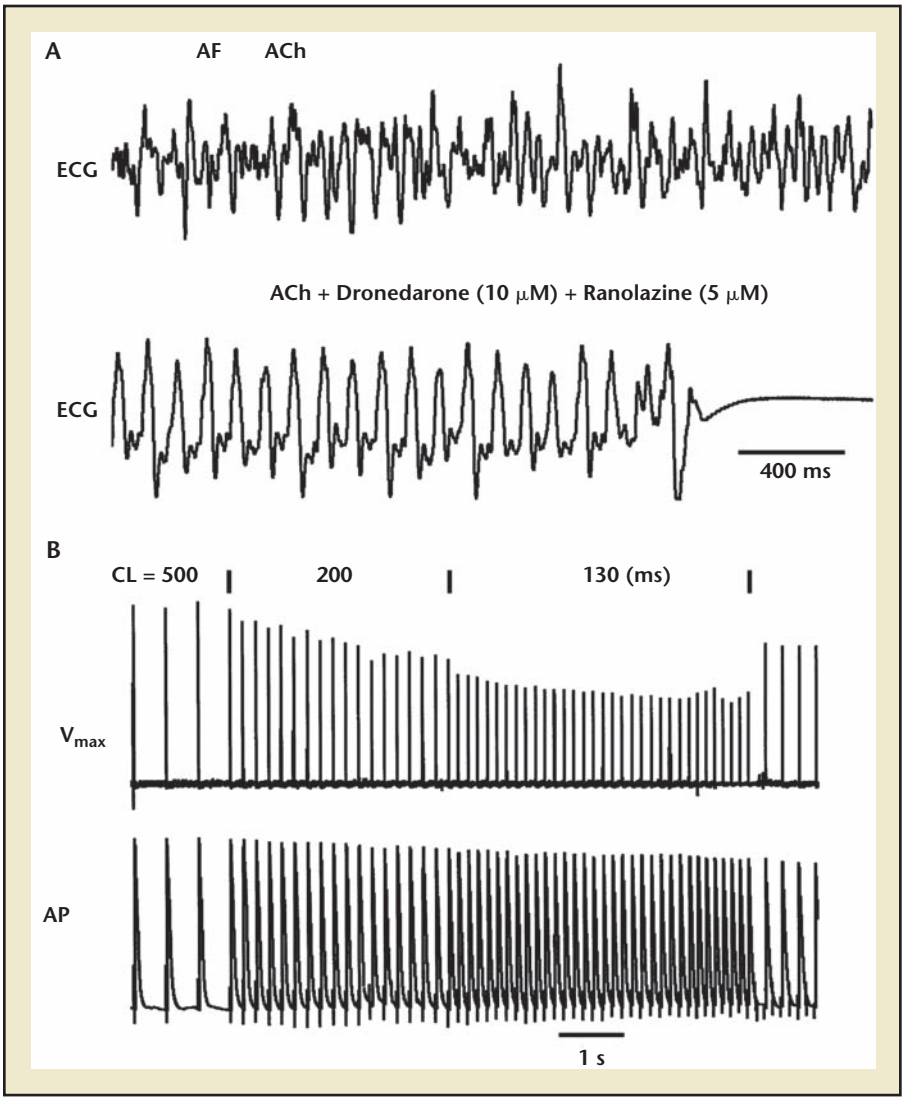

Figure 1. *Effect of dronedarone and ranolazine to suppress AF. The combination of dronedarone (10 μmol/L) and ranolazine (5 μmol/L) is effective in terminating persistent AF and/or preventing its induction in coronary-perfused right atria.* **(A)** *Persistent Ach (0.5 μmol/L)-mediated AF is terminated by the drug combination. AF is initially converted to flutter and then to sinus rhythm.* **(B)** *The combination of dronedarone and ranolazine prevents rapid-pacing induction of AF after pretreatment with Ach (1 μmol/L), likely because of depression of the sodium channel (see reduction of maximal rate of rise of the AP upstroke). Acceleration of pacing rate from a CL of 500 to 130 ms leads to failure of a 1:1 response. Ach, acetylcholine; AF, atrial fibrillation; AP, action potential; CL, cycle length; ECG, electrocardiogram. Reprinted from* J Am Coll Cardiol. *Vol. 56, Burashnikov A et al. Synergistic effect of the combination of ranolazine and dronedarone to suppress atrial fibrillation. Pages 1216-1224, © 2010; with permission from Elsevier.*

dronedarone can also exert a similar effect when combined with ranolazine, similar to those observed with amiodarone coadministration. At Westside Medical Associates (Los Angeles, CA), we have collected a small case series of ranolazine coadministration with either amiodarone or dronedarone that has shown a greater impact on maintaining normal sinus rhythm in patients with persistent AF who are refractory to monotherapy. We await randomized clinical trial data in humans to determine whether the findings observed in the animal model can be replicated in humans with AF prior to any recommendation of the use of this combination therapy. Issues that need to be addressed include the pharmacokinetic impact of ranolazine on dronedarone metabolism, along with data showing safety and efficacy. ■

References

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