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Ranolazine for Atrial Fibrillation: Too Good to be True?

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Introduction

Several management options for patients with symptomatic atrial fibrillation (AF) available today were not even in the realm of discussion two decades ago. These advances, however, have primarily involved invasive management options for patients with drug refractory arrhythmia.[1-3] After the recognition that electrical isolation of the thoracic veins benefits patients with paroxysmal AF, a slew of more involved ablative techniques evolved.[4-8] Major breakthroughs in antiarrhythmic therapy, however, have not paralleled this meteoric development of invasive techniques. The drive for invasive procedures has, in fact, been widely based on the lack of availability of simple, effective, and safe pharmacological options for AF.[9-11] The introduction of dronedarone into clinical practice represented a recent addition to antiarrhythmic therapy options for use in the management of patients with AF. This agent is an analogue of amiodarone but devoid of the iodine moiety which allows its use without the well-recognized and dreaded organ toxicity associated with long-term use. Nevertheless, a significant need exists for a drug with limited side effects that can be used for symptomatic intermittent AF without the need for daily chronic use, fear of organ toxicity, and concern regarding proarrhythmia in patients with structural heart disease.

In this issue of JAFIB, Murdock et al. report their findings on using ranolazine, an antianginal agent, for the acute termination of AF in 35 patients. They performed a retrospective chart review involving two centers who had been independently using ranolazine as an "off-label" agent to convert recent onset AF to sinus rhythm.[12, 13] The study patients had AF between 3-48 hours, were not on any other antiarrhythmic agent, and received 2000 mg of ranolazine as a single dose. If AF terminated within 6 hours, its use was considered a success. There was a 71% (25/35) conversion rate of AF within a 6-hour timeframe. Importantly, 86% of these patients had structural heart disease and no major complications (1 patient with severe constipation), specifically, no proarrhythmia was noted. Based on these findings, the authors suggest further studies to determine if ranolazine can be a potential "pill-in-the-pocket" option for managing symptomatic AF. They note the success rate that they observed is comparable to what has been observed with propafenone or flecainide,[14-17] the most frequently used pharmacological cardioversion of AF.

Why Ranolazine?

Ranolazine is an agent presently approved for use and is increasingly being utilized as an antianginal agent. The drug inhibits some late sodium-channel current and thus decreases calcium overload, the underlying mechanism for abnormal afterdepolarizations. Since early recurrences

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of AF often involve arrhythmia arising from the pulmonary veins[2, 18, 19] and triggered activity has been proposed as a likely mechanism for these arrhythmias,[20, 21] ranolazine is theoretically a candidate agent for AF. In a few small clinical studies, ranolazine has appeared to suppress AF.[22-24] In the MERLIN trial, ranolazine was associated with reduction in several arrhythmias (atrial and ventricular) including new onset AF.[24, 25] Further, ranolazine is devoid of any known proarrhythmic potential and does not suppress sinus node or AV nodal function. Because of this, slow conduction would likely not result in organization of AF to chronic macroreentrant atrial tachycardias. Although not developed as an antiarrhythmic agent, ranolazine is not alone in taking this route to being a potential antiarrhythmic drug based on theoretical considerations and limited clinical data.[26-28]

Prior to deciding whether ranolazine does, in fact, represent a safe effective agent for AF management, we must examine the present limitations with AF therapy as well as the limitations of the present report by Murdock et al.

1. Intermittent AF. Radiofrequency ablation is relatively successful often as a single procedure to manage patients with paroxysmal AF. These patients have frequently occurring, self-terminating episodes of arrhythmia that typically arise from the pulmonary veins, and electrical isolation of these veins is a largely effective and safe option for symptom management. These patients commonly have coexisting dyslipidemia or hypertension. HMG-CoA reductase inhibitors (statins) and inhibitors of the renin-angiotensin system (angiotensin-converting enzyme inhibitors and angiotensin II–receptor blockers) may reduce the risk of developing AF.[29, 30]

In patients with persistent or chronic AF, especially where cardioversion is ineffective, long-term drug therapy including rate control and anticoagulation approaches can be effective as well.[31, 32]

However, a unique set of patients are those who have intermittent AF but the episodes do not terminate spontaneously. Nevertheless, cardioversion (electrical or pharmacological) is effective in relieving the index episode, and recurrence may not occur for several months or years. For these patients, commitment to long-term daily drug therapy or immediate invasive procedures appears an inappropriate and inadequate management strategy. "Pill-in-the-pocket" as well as atrial defibrillator placement-based therapies were developed to target this patient population. However, atrial defibrillators are rarely used since the pain associated with shocks adversely impacts quality of life.[33, 34]

2. AF in the setting of structural heart disease. A major limitation with present therapies for AF involves problems with using pharmacologic agents in patients with structural heart disease. Class 1c agents (flecainide, propafenone, etc.), the most commonly used drugs in patients with normal hearts, are contraindicated with significant structural heart disease because of the potential of inducing proarrhythmic, malignant ventricular arrhythmia.[35, 36] AF, however, frequently occurs in the setting of structural heart disease including congestive heart failure, valvular disease, and coronary artery disease.[1] Drug treatment options are limited for this patient population. Amiodarone is commonly used, but long-term accumulation of the drug and induction of organ toxicity (pulmonary, hepatic, skin, etc.) essentially rule out this drug for use in younger patients. Dofetilide can also be used as AF management in structural heart disease. Unfortunately, the drug's exquisite dependence on normal renal function and effects on ventricular repolarization make it difficult to use this agent in sick patients who are at risk for renal dysfunction, etc. Dronedarone with its recent approval is a major new option for managing AF in patients with structural heart disease. However, this agent does have effects on sinus and AV nodal function (this effect may be beneficial in managing symptoms as well) and needs to be used on a daily basis indefinitely.

Ranolazine, if found to be effective in larger, future studies, is potentially an attractive agent for these patient populations based on the lack of observed proarrhythmia and the absence of major side effects.

3. Pulmonary vein arrhythmogenecity. Presently available antiarrhythmic agents increase refractoriness, slow cardiac conduction, or, in some instances, suppress enhanced automaticity.[20, 21, 37, 38] The recent understanding of the unique role of the pulmonary and other thoracic veins has, in turn,

resulted in the need for agents that may be specifically useful in suppressing triggered arrhythmias from the thoracic veins that result in recurrence of AF. Although it is much too early to know whether ranolazine is such an agent, it may be that discussion of such agents begins to fill this void in our antiarrhythmic drug therapy armamentarium.

Too Good to be True?

The authors acknowledge major limita tions in their study that are worth reiterating.

Their study is an uncontrolled, non-placebo-controlled retrospective chart review. The need for placebo control has been well emphasized since the nature of paroxysmal AF involves self termination of arrhythmia in a majority of patients. Although the authors compare their data with historical placebo conversion rates, the type of patients including the duration of arrhythmia, prior episodes, and concomitant illnesses may have been quite different. Thus, in addition to a placebo arm, controlling also in a prospective fashion for well-recognized predictors of successful therapy for AF is essential. The authors did not seek or obtain IRB approval for their study, and they state that this was not required because of the retrospective chart review nature of their study. Future trials with high-dose ranolazine will require careful patient consent and institutional approval given the lack of efficacy or safety data with high-dose use, especially in the arrhythmia population. Another issue that requires clarification but is limited by their study design has to do with why ranolazine would be specifically effective for acute cardioversion. The theoretical basis for studying this agent in AF involves its potential ability to prevent early recurrence from triggered pulmonary vein arrhythmia. Why, therefore, should this agent be useful in terminating existing AF? Does this suggest that in some patients the continued persistence of AF reflects the persistence of a focal triggered arrhythmia?

This report by Murdock et al. does generate considerable thought and is potentially an important hypothesis-generating report. With this and other recent retrospective data, there is likely enough evidence to warrant carefully controlled studies before we know whether ranolazine is the promised drug or is just too good to be true.

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