

Electrophysiological Changes of the Atrium in Patients with Lone Paroxysmal Atrial Fibrillation

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Abstract

Background : The “Pill-in-Pocket” (PIP) is an approach to atrial fibrillation (AF) where oral anti-arrhythmics at 75% to 100% of the normal daily dose, given as a single dose, is used to convert recent-onset AF. Pro-arrhythmic risk has limited this approach to patients without structural heart disease (SHD). Ranolazine is an anti-anginal agent, which inhibits the abnormal late Na⁺ channel current resulting in decreased Na⁺/Ca⁺⁺ overload. This inhibits after-depolarizations and reduces pulmonary vein firing, which have been implicated in the initiation and propagation of AF. Ranolazine increases atrial refractoriness and has no known pro-arrhythmic effects. Ranolazine is routinely given to patients with SHD. The ability of Ranolazine to terminate AF in man has not been described but if useful could be a safer PIP agent with application in the presence or absence of SHD. We describe our experience using oral Ranolazine to convert new or recurrent AF.

Method : 2000 mg of ranolazine was administered to 35 patients with new (16 patients) or recurrent (19 patients) AF of at least 3 but not greater than 48 hours duration. Clinical features, echocardiographic data, and SHD were noted. Success was defined as restoring sinus rhythm within 6 hours of Ranolazine.

Results : All but 4 patients had some form of SHD. Twenty-five patients were in the hospital, 5 were in the office, and 5 were at home at the time Ranolazine was administered. Twenty-five of 35 patients converted to sinus rhythm. No pro-arrhythmic effects, hemodynamic instability, adverse rate effects, or perceived intolerance were noted. The 71% conversion rate was comparable to other reported PIP protocols and much higher than reported placebo conversion rates.

Conclusions : High dose oral Ranolazine shows utility as a possible safe agent to convert new or recurrent AF. Larger placebo-controlled studies would appear to be warranted.

Key Words : Atrial fibrillation, ranolazine, conversion, anti-arrhythmic therapy, anti-arrhythmic agents.

Introduction

Paroxysmal atrial fibrillation (AF) frequently requires intervention to restore sinus rhythm.^{1,2} Transthoracic electrical cardioversion is the most

effective method for terminating AF.³ Anti-arrhythmic agents may be used in some patients to convert them to normal sinus rhythm.⁴⁻¹³ Pro-arrhythmic concerns have limited the usefulness of anti-arrhythmic therapy in the un-monitored

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setting^{6,8,9,14,15} as has, in some patients, bradycardic concerns and concerns about the potential transition of AF to atrial flutter with a rapid ventricular response when class IC or IA agents are used. However, in properly chosen patients, those without structural heart disease (SHD), high dose oral anti-arrhythmic agents (usually 75 to 100% of the normal daily dose of propafenone or flecainide given as a single oral dose) may effectively and safely convert 70-80% of patients with recent-onset, new or recurrent, AF¹⁰⁻¹³ in an out-patient setting. This may be at home, unmonitored, in patients at lowest risk or in those who have previously shown both efficacy and tolerance with this approach. This "Pill-in-Pocket" approach has allowed these patients to effectively treat themselves on an "as needed" basis when AF occurs without the need to immediately seek medical attention or use anti-arrhythmic therapy on a chronic basis.

Many cases of AF appear to originate and be propagated from ectopic activity originating at the junction of the left atrium and the pulmonary veins.¹⁶ The mechanisms responsible for the abnormal impulse activity have been the source of several investigations.¹⁷⁻²³ Triggered activity may be particularly important.¹⁹⁻²³

Ranolazine is an anti-anginal agent, which inhibits the normal and abnormal late Na⁺ channel current in the ventricle and the peak Na⁺ channel current in the atrium.²⁴⁻²⁶ By this inhibition, it affects intracellular calcium handling, producing an energy sparing effect.²⁴ Ranolazine induces post repolarization refractoriness in atrial tissue and is a potent inhibitor of after depolarizations produced by a number of mechanisms,²⁵⁻²⁸ an effect that could reduce pulmonary vein firing. As such, ranolazine should prove to be particularly useful in the treatment of AF. Indeed, in the Holter monitor data from the MERLIN trial, ranolazine was associated with a reduction in the incidence of several arrhythmias, including new episodes of AF.^{29,30} We have extended these observations to show that ranolazine can be successfully employed as an anti-arrhythmic agent and can be particularly useful in AF.³¹⁻³³

Since ranolazine is devoid of known pro-arrhythmic effects, is well tolerated, is not an inducer of sinus node dysfunction or atrial flutter, and can be given to patients with SHD, it could prove to be an

ideal agent for the "Pill-in-Pocket" approach to AF if it were effective in converting patients with AF to sinus rhythm. Indeed, in preliminary observation from a single center, we described the safety and feasibility of using ranolazine for this purpose in a limited number of patients.³³ The purpose of this report is to significantly expand upon that experience with data from more than one center and including several additional patients with and without SHD. This was a retrospective analysis of our experience using ranolazine for this purpose. Institutional review board approval is not required for retrospective chart review.

Study Population

Thirty-five patients with a known duration of AF of greater than 3 hours but less than 48 hours encountered in our clinical practices had been treated with oral ranolazine in an attempt to convert their AF. Each patient had been informed that this was an "off label" use of ranolazine and its ability to convert him/her to sinus rhythm was unknown but that its safety profile in patients with SHD made it appear to be a reasonable consideration. In 2009, the investigators, learning of each other's use of ranolazine in this manner, decided to do a retrospective chart review of their combined experience. The age and gender was noted for each patient. Echocardiographic data, and other cardiac test results, when available, including left ventricular anatomy and function, left atrial size, presence or absence of ischemic disease was gathered. Also any other associated cardiovascular disorder such as hypertension or diabetes was noted. The history of the AF problem (first recognized episode or recurrent) was also determined for each patient. Finally, the location of the first ranolazine treatment (home, office, hospital) was noted.

The treatment with ranolazine consisted of the administration of 2000 mg of ranolazine. In 34 patients this was given as a single dose. One patient received a 1000 mg dose followed by a second 1000 mg 2 hours later. This dosage represented 100% of the usual maximum daily dose for angina. The treatment was deemed successful if the interval between administration of ranolazine and conversion of AF to sinus rhythm was 6 hours or less.¹¹ Each patient in the hospital or office was also observed for side effects, such as symptomatic hy-

potension (systolic blood pressure <100mm Hg), symptomatic bradycardia after restoration of sinus rhythm, dyspnea, presyncope, syncope, or conversion to atrial flutter or atrial tachycardia. Patients at home when they took the ranolazine were later questioned for adverse side effects. In addition all patients were questioned regarding any worsening of the symptoms related to AF and possible side effects associated with ranolazine such as constipation, light headedness or nausea.

Patients were excluded from consideration of this approach if they were on any other anti-arrhythmic agent other than beta or calcium channel blockers, had a history of second- or third-degree atrioventricular block, or bradycardia–tachycardia syndrome (unless paced).

Results

Table 1 describes the clinical characteristics of the patients included in this study and the setting in which ranolazine was administered. Echocardiographic data was available on all but 1 patient. Note that the majority of patients had SHD (86%) and left atrial enlargement (69%). The one patient without echocardiographic data had a normal electrocardiogram, no history of SHD, nor any reason to suspect it.

Note: most patients were in the hospital when ranolazine was administered including all patients with new onset AF. In the hospitalized patients, AF was not present at the time of admission but occurred during the course of treatment for other issues. One hospitalized patient was recruited immediately after he had failed electrical cardioversion for new AF. In 5 patients with a history of recurrent AF, the AF occurred in the outpatient setting and the patients called our facilities with recurrent palpitations. These patients were seen in the office where the AF was confirmed by an electrocardiogram. Five patients with well-tolerated paroxysmal AF were at home when ranolazine was administered. Each of these patients had demonstrated that they were aware of their arrhythmia because of palpitations but were hemodynamically stable (i.e., without symptoms such as dyspnea, presyncope, or syncope) during the episodes.

Twenty-five of 35 patients with new or recurrent AF

converted to sinus rhythm within 6 hours of ranolazine administration. Ranolazine was very well tolerated in this setting. No patient experienced any cardiovascular side effects or worsening of AF symptoms. One patient experienced severe

Table 1 | Patient Characteristics

Characteristic	No. (%)
Total Patients	35 (100)
Successful conversion	25 (71)
Age	72 ± 7
Sex	
Male	22 (63)
Female	13 (37)
Type of A-Fib	
Initial	16 (46)
Paroxysmal	19 (54)
LVEF (%)	52 ± 10
≤45%	12 (34)
Structural Heart Disease (SHD)	
Yes	31 (86)
No	4 (14)
Type of SHD:	
CAD	15 (43)
MVP	4 (11)
LVH	8 (23)
LAE	24 (69)
Recent MI	3 (9)
MR/MS	4 (11)
AS	4 (11)
Concomitant Conditions	
HTN	18 (51)
Diabetes	1 (3)
CHF	5 (14)
COPD	3 (9)
Pacemaker	2 (6)
Marfan's Syndrome	1 (3)
None	4 (11)
Location of 1st Dose	
Hospital	25 (71)
Office	5 (14)
Home	5 (14)

AS: aortic stenosis, CAD: coronary artery disease, CHF: congestive heart failure, COPD: chronic obstructive lung disease, LAE: left atrial enlargement, LVEF: left ventricular ejection fraction, LVH: left ventricular hypertrophy, MVP: mitral valve prolapse, MR: mitral regurgitation, MS: mitral stenosis.

constipation lasting about 36 hours each time he used ranolazine. Six patients with recurrent AF continue to use ranolazine on a “pill in pocket” basis. One other patient stopped using it after its initial effectiveness abated and now has persistent AF.

Discussion

We found that 2000 mg of oral ranolazine, when administered as a single oral dose, was reasonably effective and Ranolazine was very well tolerated. Twenty-five of 35 patients with new or recurrent AF converted to sinus rhythm within 6 hours of dose administration. The conversion rate we observed with ranolazine was similar to the 6 to 8 hour conversion rates previously reported with high dose oral “pill in pocket” propafenone or flecainide¹⁰⁻¹³ and higher than the 39% placebo 8-hour conversion rate noted by Capucci et al.¹³ In none of our patients was ranolazine associated with any worsening of the symptoms from AF prior to conversion or did any adverse cardiovascular effects develop. Although it is likely that some of these patients would have converted spontaneously without ranolazine, the high rate of conversion strongly suggests that ranolazine was instrumental in the conversion process. These results are in agreement with other reported observations with this agent. Ranolazine has been shown to suppress AF in a few, mostly small, clinical studies,^{29, 30, 32} none of which, however, studied pharmacologic conversion as the therapeutic goal. In a canine study, ranolazine prolonged atrial refractory periods in a use dependent manner, which should give it anti-fibrillatory effects.²⁶ Additionally, ranolazine is an inhibitor of triggered activity which may be important mechanism underlying to initiation and potentiation of AF.^{19-23, 25-28} Finally the time course of the observation is consistent with our prior experience in which we reported that ranolazine begins to have significant anti-arrhythmic effects within a few of hours of administration.³¹ Our current report adds important additional information to the developing profile of ranolazine as a clinically useful and relevant anti-arrhythmic agent.

Limitations

The small number of patients in our report cannot be assumed to reflect the certain reproducibility of our observations, although there is no basic or

clinical data on which to question them. Additionally, this was a real life experience with ranolazine. Like all real life clinical decision making regarding anti-arrhythmic therapy, we gauged the effectiveness of ranolazine based upon the observed clinical response. Additional data from a continuous ECG monitoring protocol would be of interest. In addition, because our experience was not placebo controlled, the number of patients who may have converted spontaneously within the 6 hours period is unknown. Indeed it seems very likely that some would have.¹⁰⁻¹³ But our conversion rates approximate that with class IC agents which have been proven to result in higher and more rapid conversion rates than placebo.³⁴ This observation serves as a useful pilot study demonstrating the feasibility of this approach.

In Summary

We found that high dose oral ranolazine (2 grams) was very well tolerated and shows promise as an anti-arrhythmic agent that can be useful in facilitating the conversion of AF. This has implications for a possible broad “pill-in-pocket” approach using ranolazine. Given the apparent electrophysiologic safety of ranolazine and the ability to use it in patients with SHD where current class I agents used as “pill in the pocket” therapy cannot be used, such an option could have enormous clinical and economical implications. Further investigations are warranted to explore this novel use for this medication.

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