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Ranolazine as Antiarrhythmic Agent

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Abstract

Ranolazine which has been approved for use as an anti-anginal agent has been shown to have anti-arrhythmic properties both in experimental and clinical studies. Several case studies have shown the use of ranolazine in the treatment of atrial fibrillation, some even as a 'pill in the pocket' approach. MERLIN-TIMI 36, a randomized study of acute coronary syndrome, showed lower incidence of ventricular arrhythmias in the ranolazine arm. The most important anti-arrhythmic mechanism of ranolazine is thought to be mediated by atrial-selective inhibition of peak sodium current (I_{NaL}) and inhibition of late I_{Na} in both atria and ventricles. The recent reclassification of anti-arrhythmic agents has designated drugs with this action in Class Id. There is clinical and experimental evidence for the potential use of ranolazine in congenital long QT syndrome 3. The recent RAID trial, a randomized evaluation of ranolazine in high risk patients with implantable cardioverter defibrillator and either ischemic or non-ischemic cardiomyopathy showed a marginally significant reduction of recurrent ventricular tachycardia and fibrillation. The potential risk of ranolazine-induced torsade de pointes in view of mild prolongation of QT interval has not been well confirmed, with only a single case report suggesting possible association. But the patient had other confounding factors including treatment with fluoxetine, amiodarone and diuretics causing hypokalemia and hypomagnesemia which are well known to cause torsade de pointes.

Keywords: ranolazine, antiarrhythmic agent, class Id agent, atrial fibrillation, ventricular arrhythmias

Introduction

Amiodarone which was initially introduced as an antianginal agent later became an exclusive anti-arrhythmic agent. The story of ranolazine seems headed in the same direction. Ranolazine was approved as an anti-anginal agent for treatment of chronic stable angina by the US Food and Drug Administration (FDA) in 2006. Since then there have been case series and clinical trials documenting an antiarrhythmic role for ranolazine [1-3]. One study even demonstrated a synergy between amiodarone analogue dronedarone and ranolazine [3]. Metabolic Efficiency with

Ranolazine for Less Ischemia in Non ST-Elevation Acute Coronary Syndrome Thrombolysis in Myocardial Infarction 36 (MERLIN-TIMI 36) study which randomized non-ST-elevation acute coronary syndrome to ranolazine or placebo found a lower incidence of arrhythmia in the active treatment arm [4]. A recent paper presenting a modernized classification of anti-arrhythmic agents has designated late sodium current inhibitor ranolazine as a Class Id agent [5].

In this review we evaluate the evidence supporting use of ranolazine for the treatment of atrial and ventricular arrhythmias.

Electrophysiological basis of antiarrhythmic effect of Ranolazine

The electrophysiological basis for the antiarrhythmic effects of ranolazine was reported even before the FDA approval of ranolazine as an antianginal agent [6]. This was in spite of the fact that ranolazine produces modest prolongation of the QT interval [7], although not resulting in development of torsade de pointes (TdP). Studies involving canine ventricular tissue showed that ranolazine has ion channel effects similar to those observed with chronic amiodarone therapy. Late sodium current, rectifier currents (IKr and Iks) and calcium currents were reduced. But the effect of ranolazine on calcium current is very weak and that would explain the lack of effects on contractility, atrioventricular nodal conduction and heart rate. Ranolazine was shown to suppress early after depolarization (EAD) and transmural dispersion of repolarization (TDR) [6].

There is a difference between the effect of ranolazine on atrial and ventricular myocytes. While ranolazine blocks both peak and late sodium currents in atrial myocytes [8,9], it predominantly blocks the late sodium current in ventricular myocytes. Ranolazine has structural similarity to lignocaine molecule, which is the reason it blocks sodium channels in a use dependent manner similar to local anaesthetics by interacting with the local anaesthetic receptor site on the NaV1.5 channel [10].

Important mechanism by which ranolazine exerts its anti-arrhythmic effect on the ventricles is by the inhibition of late sodium current. This in turn reduces the sodium dependent intracellular calcium overload which contributes to suppression of afterdepolarization activity [11].

Ranolazine in atrial fibrillation

One of the earliest reports of the role of ranolazine in atrial fibrillation (AF) was a case series published in 2008 [1]. Murdock DK et al. used it in 7 patients who developed AF within hours to days of ablation and / or failure of other anti-arrhythmic agents. Four of them had no recurrence of AF while on ranolazine, two did not respond and one had a delayed recurrence. The same group of authors reported a “Pill in the pocket” approach to AF using ranolazine the next year [2]. Thirteen of their 18 patients converted to sinus rhythm without any proarrhythmic effects following a single dose of 2000 mg. All but one of their patients had some form of structural heart disease and all but 2 had left atrial enlargement. The 72% conversion rate was comparable to other reported protocols for “pill in the pocket” approach.

Ranolazine-induced inhibition of peak INa in the atria, reduces atrial excitability and effective refractory period. This prevents rapid activation of the atria in AF. The blockade of IKr by ranolazine delays atrial repolarization thus abbreviating the diastolic interval. It is during the diastolic interval that much of the recovery of the sodium channel from drug block occurs. As a result recovery of the sodium channel from ranolazine block is impaired, resulting in greater accumulation of block and reduction of INa. The maintenance of a diastolic interval in the ventricle, even at rapid rapids of activation, accounts for the lesser effect of ranolazine in the ventricles when compared with the atria. Block of both peak and late sodium current by ranolazine in the atria reduces intracellular calcium activity which in turn suppresses afterdepolarization-mediated triggers of AF [11].

A recent systematic review of the role of ranolazine in the treatment and prevention of AF found a modest beneficial effect of ranolazine for prevention or treatment of atrial fibrillation [12].

Enhancement of effect of amiodarone on AF by ranolazine

Ranolazine added to intravenous amiodarone was found to enhance the efficacy of the latter in converting recent onset AF [13]. 121 patients with recent onset AF received either amiodarone infusion alone or amiodarone infusion and a single oral dose of ranolazine 1500 mg. Conversion rate at 24 hours was higher in those who received ranolazine (87% vs 70%, $P=0.024$). Time to conversion was also shorter in those who received ranolazine along with amiodarone (10.2 ± 3.3 vs. 13.3 ± 4.1 h; $P = 0.001$). In a subgroup analysis, they noted that those with left atrial diameter above 46 mm responded to the combination (81% vs. 54%; $P = 0.02$), while there was no difference between the two groups in those with left atrial diameter of 46 mm or lower ($P=0.77$). This study confirmed the findings of an earlier pilot study involving 51 patients from the same center [14].

Another single blinded randomized trial evaluated the effect of ranolazine on post-operative AF after coronary artery bypass graft surgery [15]. 375 mg twice daily of ranolazine was added to intravenous amiodarone (study group) and compared with intravenous amiodarone alone (control group). Though this was a small study with a total of only 41 patients, it could document a significantly faster conversion of post-operative AF (19.9 ± 3.2 vs 37.2 ± 3.9 hours, $P < 0.001$) when ranolazine was combined with intravenous amiodarone.

Synergy between ranolazine and dronedarone in AF

A Study to Evaluate the Effect of Ranolazine and Dronedarone When Given Alone and in Combination in Patients with Paroxysmal Atrial Fibrillation (HARMONY Trial) [3] showed a synergy between the anti-arrhythmic actions of ranolazine and dronedarone. 750 mg twice daily or ranolazine was tested with 150 mg twice daily and 225 mg twice daily of dronedarone in 134 patients with paroxysmal atrial fibrillation (AF) and implanted pacemakers. The AF burden was continuously assessed by the pacemaker electrogram recordings. It was noted that neither placebo nor either of the two drugs alone reduced the AF burden significantly. The higher dose combination reduced AF burden by 59% compared to placebo while the lower dose combination reduced AF burden by 43%. The combinations were well tolerated by the participants. Lower doses of dronedarone were chosen in this study to reduce its negative inotropic effect.

The experimental basis for HARMONY trial was provided by a previous canine study involving isolated canine coronary perfused atrial and ventricular preparations [16]. In that study, it was shown that low concentrations of ranolazine which had weak suppression of AF independently, had a potent synergistic effect on combination. While the drugs independently could only prevent induction of AF in 17% and 29% respectively, the combination could prevent induction of AF in 90% of the preparations studied.

Role of ranolazine in congenital long QT syndrome type 3

It is well known that ranolazine inhibits late sodium current [6]. Congenital long QT syndrome type 3 (LQT3) is due to excessive late sodium current during phase 3 of the action potential, secondary to a mutation in the cardiac sodium channel gene SCN5A [17]. Hence the role of ranolazine in LQT3 was studied in experimental and clinical settings [18]. In the clinical arm of the trial involving 8 patients evaluated over 22.8 ± 12.8 months, ranolazine was found to shorten the corrected QT interval (QTc) from 509 ± 41 to 451 ± 26 ms ($P=0.012$). QTc abbreviation was less prominent during extreme nocturnal bradycardia. This study was prompted by a previous short-term study involving 5 patients with LQT3, which had shown abbreviation of QTc by 26 ± 3 ms following an

8-hour intravenous infusion of ranolazine [19]. The added advantage noted with ranolazine treatment for LQT3 was that none of the patients developed ECG pattern suggestive of Brugada syndrome. Earlier it had been reported that patients with LQT3 treated with sodium channel blockers can develop Brugada syndrome [20]. One important limitation noted in the report on ranolazine for LQT3 [18] was that there was only one case with documented TdP in this series. Hence the role of ranolazine in preventing arrhythmias in LQT3 could not be documented. Moreover, QTc values above 500 ms were noted during extreme nocturnal bradycardia even while on treatment with ranolazine. These values are usually associated with TdP, though no TdP occurred during the study period.

Can ranolazine cause TdP?

Mild QT prolongation produced by ranolazine is due to its effect to inhibit the rapidly activating component of the delayed rectifier potassium current (IKr), encoded by the human ether-a-go-go-related gene (hERG) [21]. The protective effect of ranolazine against TdP is thought to be the potent inhibition of late sodium current which opposes the prolongation of action potential and increase in transmural dispersion of repolarization induced by IKr block [22]. Another reason proposed is that the kinetics of both blocking and unblocking of the channel by ranolazine is rapid [21]. This is in contrast with the slow kinetics of dofetilide for unblocking of the IKr channels.

Romero J et al [23] in a retrospective analysis of 2735 patients with prolonged QTc found 7 cases of QTc prolongation and 3 cases of TdP associated with ranolazine, which was found to be significant in univariate and multivariate analysis. But they mentioned in the limitations of their study that it is difficult to make meaningful conclusions due to the small number of patients who took this medication in their study. Moreover, their discussion was mostly focussed on methadone, which was highlighted in the title of the article.

One case of TdP with potential role for ranolazine as a contributing agent has been reported by Liu et al [24]. This elderly female was on multiple drugs including fluoxetine, amiodarone and diuretics. Ranolazine 500 mg daily was added for refractory angina. She developed multiple episodes of TdP while in hospital. An absolute causal role for ranolazine cannot be confirmed as she was on diuretics causing hypokalemia and hypomagnesemia as well a fluoxetine and amiodarone, which have been associated with TdP. Based on this report, CredibleMeds® moved ranolazine from ‘Possible Risk’ list to the ‘Conditional Risk (CR) of TdP’ list, but not to the ‘Known Risk’ list [25].

Ranolazine in ventricular arrhythmias

MERLIN-TIMI 36 showed a reduced risk of ventricular tachycardia lasting at least eight beats on one-week ECG monitoring in the first week after admission for acute coronary syndrome (5.3% versus 8.3%; $P < 0.001$) [4]. The study randomized 6560 patients admitted with non-ST-elevation acute coronary syndrome to either ranolazine or placebo. Ninety seven percent of patients in this study had ECG tracings which could analysed in a core laboratory for a pre-specified set of arrhythmias. Supraventricular tachycardia was also lower in the study group (44.7% versus 55.0%; $P < 0.001$).

Ranolazine in High-Risk Patients With Implanted Cardioverter-Defibrillators: The RAID Trial was a double-blind placebo controlled clinical trial in patients high-risk patients with an implantable cardioverter defibrillator (ICD) [26]. The patients with either ischemic or non-ischemic cardiomyopathy were randomized to receive either 1000 mg ranolazine twice daily or placebo. Ventricular tachycardia (VT) or fibrillation (VF) requiring appropriate ICD therapy of death, whichever occurred first, was the primary endpoint. Pre-specified secondary end points were ICD shock requiring VT/VF or death and recurrent VT or VF. Ranolazine did not significantly reduce the primary endpoint. But the study was underpowered to detect a difference in the primary endpoint. Pre-specified secondary analysis showed that ranolazine marginally reduced recurrent VT or VF

(hazard ratio: 0.70; 95% confidence interval: 0.51 to 0.96; $p = 0.028$), without increasing mortality.

Conclusion

Several studies have demonstrated the anti-arrhythmic role of ranolazine. Recognizing this, the new modernized classification of anti-arrhythmic agents has designated ranolazine as Class Id agent. Additional randomized trial data are needed to elevate ranolazine to the status of a dedicated anti-arrhythmic agent like amiodarone. Though a single case report has raised caution about potential role in proarrhythmia (TdP), multiple confounding factors noted in the case makes the direct causation less likely.

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