Impact of ranolazine on ventricular arrhythmias – A systematic review

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Abstract
Ranolazine is a new medication for the treatment of refractory angina. However, except its anti-anginal properties, it has been found to act as an anti-arrhythmic. The aim of our systematic review is to present the existing data about the impact of ranolazine in ventricular arrhythmias. We searched MEDLINE and Cochrane databases as well clinicaltrials.gov until September 1, 2017 to find all studies (clinical trials, observational studies, case reports/series) reported data about the impact of ranolazine in ventricular arrhythmias. Our search revealed 14 studies (3 clinical trials, 2 observational studies, 8 case reports, 1 case series). These data reported a beneficial impact of ranolazine in ventricular tachycardia/fibrillation, premature ventricular beats, and ICD interventions in different clinical settings. The existing data highlight the anti-arrhythmic properties of ranolazine in ventricular arrhythmias.
Introduction

Ranolazine is a new medication indicated for the cases of refractory angina despite conventional anti-ischemic regimens. Its anti-ischemic effects have been demonstrated by several clinical trials. Additionally, it exerts modulatory effects on ion channels that have been similarly observed after chronic amiodarone use, such as reductions in $I_{Kr}$, $I_{ks}$, late $I_{Na}$, and $I_{Ca}$. Consequently, ranolazine appears to have beneficial roles in both atrial and ventricular arrhythmias. The aim of our systematic review is to present the existing data about the impact of ranolazine in ventricular arrhythmias.

Methods

2.1 Search strategy

Two independent investigators (G.B. & G.T.) searched MEDLINE and Cochrane databases as well clinicaltrials.gov, without year or language restriction or any other limitations, until September 1, 2017. The following algorithm was used: “ranolazine AND arrhythmias.” Furthermore, the reference list of all included studies, as well as relevant review articles, was also manually searched.

2.2 Study selection

2.2.1 Inclusion/exclusion criteria

The inclusion criteria were clinical trials, observational studies, case series, or case reports that reported data about the impact of ranolazine on ventricular arrhythmias. The exclusion criteria were studies that included only data on atrial arrhythmias, reported data about the impact of ranolazine in electrophysiologic properties only, or that involved experiments in animal models.

2.3 Data extraction

The following information was extracted for each study: (i) publication details (first author’s last name, journal, year of publication), (ii) general characteristics of the study (country of origin, follow-up duration, number of patients included), (iii) characteristics of the study population [age, gender, type of cardiomyopathy, left ventricular ejection fraction (LVEF), ranolazine dosage, concomitant use of other anti-arrhythmic medications], and (iv) the reported outcome about the impact of ranolazine in ventricular arrhythmias.

Results

A total of 14 studies, which reported data about the impact of ranolazine in ventricular arrhythmias, included in our systematic review (Figure 1). Of these, 2 were randomized controlled trials (MERLIN-TIMI 36 and RAID), 1 was a randomized crossover trial (RYPPLE), 2 were observational studies, 1 was a case series, and 8 were case reports (Table 1).

The included observational studies and case reports/series showed that ranolazine may have a beneficial role in reducing premature ventricular complexes (PVCs), ventricular tachycardia (VT), and ventricular fibrillation (VF) episodes as well appropriate implantable cardioverter-defibrillator therapies. According to MERLIN-TIMI 36 trial, ranolazine suppresses ventricular arrhythmias during the first week after admission for non-ST elevation acute coronary syndrome, which can decrease the incidence of sudden cardiac death.

Additionally, the RAID trial showed that ranolazine can significantly decrease VT episodes requiring antitachycardia pacing (ATP) compared to placebo patients while did not show a significant difference in the combined endpoint VT/VF or death. In regard to recurrent events, ranolazine showed a significant decrease in recurrent ventricular arrhythmias requiring ICD therapy. Finally, the RYPPLE trial showed that ranolazine can reduce complex ventricular arrhythmias compared to placebo.

The baseline characteristics and the main outcomes of the included studies are summarized in Table 1.

Discussion

Our systematic review showed that ranolazine appears to have a beneficial effect in reducing the incidence of ventricular arrhythmias. This is consistent with its ventricular effects through inhibition of the late inward sodium current $I_{Na}$ while possessing greater potency in modulating peak $I_{Na}$ in atrial cardiomyocytes. Increased late $I_{Na}$ leads to Ca overload through Na/Ca exchange in the reverse mode, leading with that way in electrophysiologic instability with action potential duration prolongation, early afterdepolarizations, and delayed afterdepolarizations.

Additionally, ranolazine leads to a reduction in the transmural dispersion of repolarization response to agents and physiologic conditions that reduce the repolarization reserve with a preferential abbreviation of midmyocardial cell action potential duration (where late $I_{Na}$ is most prominent). Furthermore, ranolazine inhibits the $I_{Kr}$, which leads to action potential prolongation in the ventricles. Thus, the net effect of ranolazine is determined by the relative magnitude of late $I_{Na}$ (inward) and $I_{Kr}$ (outward) currents during the repolarization period. Furthermore, $I_{kr}$ inhibition is the reason of the QT interval prolongation caused by ranolazine. Another possible mechanism for its beneficial role in arrhythmias is the anti-ischemic properties. Moreover, ranolazine is a weak inhibitor of L type calcium channel current ($I_{Ca,L}$), and for that reason, it does not affect significantly the myocardial contractility and heart rate at therapeutic doses.

Keywords

anti-arrhythmic drugs, ranolazine, ventricular arrhythmias, ventricular fibrillation, ventricular tachycardia
The beneficial effect of ranolazine in ventricular arrhythmias has been demonstrated in several animal studies. Specifically, ranolazine showed to reduce the doxilidile- or clonilum-induced torsades de pointes episodes in experimental models. Additionally, ranolazine can reduce the torsades de pointes liability of agents that prolong the QT interval. In long QT-2 syndrome, ranolazine was shown to prevent Ca2+ overload by stabilizing and desensitizing the ryanodine receptors, resulting in the suppression of early afterdepolarizations and torsades de pointes. Moreover, ranolazine exerted a concentration-dependent block of INa in experimental models of LQT3 harboring the D1790G mutation in SCN5A without reducing peak INa significantly. As a result, ranolazine can be safely used in LQT3 patients who are at risk for developing Brugada syndrome during sodium channel blocker therapy. In a small registry of 8 patients with LQT3, the QT-shortening effect of ranolazine persisted during the entire follow-up period of 22 months and remained during nocturnal bradycardia. The clinical significance of this finding is highlighted by the fact that cardiac arrest events in LQT3 tend to occur at night. Ranolazine has been shown to have a comparable effect with mexiletine in action potential duration shortening in LQT3 mutant cells with lower occurrence of paradoxical action potential duration prolongation. Furthermore, its beneficial role in ventricular arrhythmias has been depicted in an experimental model of Timothy syndrome (long QT-8). By contrast, in a short QT syndrome model, ranolazine reversed the induction of VF caused by pinacidil, an effect that was attributed to an increase in the effective refractory period (ERP). This would in turn increase the excitation wavelength given by the product of the ERP and conduction velocity (CV), thereby decreasing the likelihood of developing reentry. An interesting finding was the beneficial impact of ranolazine in post-VF animal models. Particularly, ranolazine showed to reduce the susceptibility to subsequent rebrilliation, but further testing in cardiac arrest models is needed. An interesting finding is that ranolazine has a potent suppressant effect on both reentrant and multifocal VF at concentrations considered therapeutic in humans.

In ischemia and ischemia-reperfusion models, ranolazine showed to reduce the incidence, frequency, and duration of VT during reperfusion subsequent to 5 min of ischemia, while it reduced the incidence and duration of VT and VF during 20 minutes of ischemia. Additionally, in another model, during 5 minutes of reperfusion, ranolazine showed to reduce except the incidence and duration of VT, the number of ventricular premature beats. Furthermore, ranolazine showed to be as effective as other anti-arrhythmic drugs (sotalol, lidocaine) to reduce reperfusion-induced ventricular arrhythmias. An interesting finding is that concurrent administration of ranolazine and drenedanone had a beneficial role in the protection against ischemia-induced vulnerability to AF and ventricular arrhythmias. The antifibrillatory effects of ranolazine in cases of severe acute coronary stenosis do not seem to be mediated by inhibition of INa but is instead attributable to inhibition of late INa. Ranolazine was found to maintain the anti-arrhythmic properties in heart failure. Specifically, it produced postrepolarization refractoriness and prevented the induction of VF episodes in a heart failure model. Mechanical stretch is an arrhythmogenic mechanism in cases of cardiac overload or dysynchronous contraction. In an experimental study, ranolazine showed to attenuate the acceleration and the complexity of VF produced by myocardial stretch. In another experimental model of pulmonary arterial hypertension, the administration of ranolazine prevented the isoprot erenol-induced VT/VF, while it has been found that play a beneficial role in the right ventricular dysfunction. Additionally, ranolazine can be used on top of class III drugs as it has been shown that it does not cause pro-arrhythmia despite a marked effect on ventricular repolarization. The beneficial role of ranolazine has also been demonstrated by experimental and human studies in atrial arrhythmias.

5 | CONCLUSIONS

Ranolazine seems to have a beneficial role in ventricular arrhythmias in different clinical settings.

CONFLICT OF INTERESTS

The authors declare no conflict of interests regarding the systematic review, but C.Th. declares consultancy fees from Astra Zeneca, and lecture honoraria from Sanofi, MSD, and Servier.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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