The Antiarrhythmic Effects of Ranolazine

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The genesis of cardiac arrhythmia can be grouped into 3 common mechanisms: abnormal automaticity, triggered activity, and re-entry. Alteration of automaticity, triggered activity, conduction, and/or refractoriness of myocardial tissue by drugs will perturb and often prevent the occurrence of arrhythmias. Ranolazine is a novel agent approved in the United States for antianginal therapy. The potential of ranolazine as an antiarrhythmic drug stems from observation of its ability to modify multiple ionic currents in cardiac cells responsible for generation of the action potential. In contrast to currently available antiarrhythmic drugs, ranolazine is well tolerated and has few side effects. Small clinical trials suggest that ranolazine may have a role in the treatment of patients with non–ST-elevation acute coronary syndrome, atrial fibrillation, long QT syndromes, and sinus node dysfunction.

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Key words: Arrhythmia • Myocardial tissue • Non–ST-elevation acute coronary syndrome • Antianginal therapy • Ranolazine

Ranolazine is a novel agent approved in the United States for antianginal therapy. The antianginal mechanisms of action may relate to alteration in cellular energy metabolism.[1] Of particular interest, however, is the observation that, at therapeutic concentrations, ranolazine possesses powerful effects modulating ionic currents in cardiac tissue. Exploitation of such properties makes ranolazine attractive as a potential antiarrhythmic medication.

This article will examine the mechanisms of arrhythmia and the electrophysiologic effects of ranolazine. It will also discuss the available clinical data regarding ranolazine in the treatment of patients with non–ST-elevation acute

coronary syndrome, atrial fibrillation, long QT syndromes, and sinus node dysfunction.

Mechanisms of Arrhythmia

The genesis of cardiac arrhythmia can be grouped into 3 common mechanisms: abnormal automaticity, triggered activity, and re-entry. Automaticity results from spontaneous depolarization during phase 4 of the action potential, and it is normally suppressed by depolarization wavefronts arising from the source with the fastest rate (usually sinus node). Pathologic automaticity may occur in states of ischemia or catecholamine excess due to a faster rate of phase 4 depolarization or partial depolarization of the resting membrane potential. Triggered activity is produced by the occurrence of early afterdepolarizations (EADs) and delayed afterdepolarizations. These membrane depolarizations occur during or after phase 3 repolarization. If they reach the depolarization threshold, another new action potential (AP) may be generated. Thus, triggered activity may itself result in arrhythmia or provide a closely coupled second depolarization that can initiate subsequent re-entry. The re-entrant mechanism of arrhythmias involves a cyclical wavefront of electrical activation that traverses a fixed path around an anatomic barrier (such as scar or valve annulus) or functional re-entry where spiral waves turn like small pinwheels and require no such anatomic substrate. Alteration of automaticity, triggered activity, conduction, and/or refractoriness of myocardial tissue by drugs will perturb and often prevent the occurrence of arrhythmias.

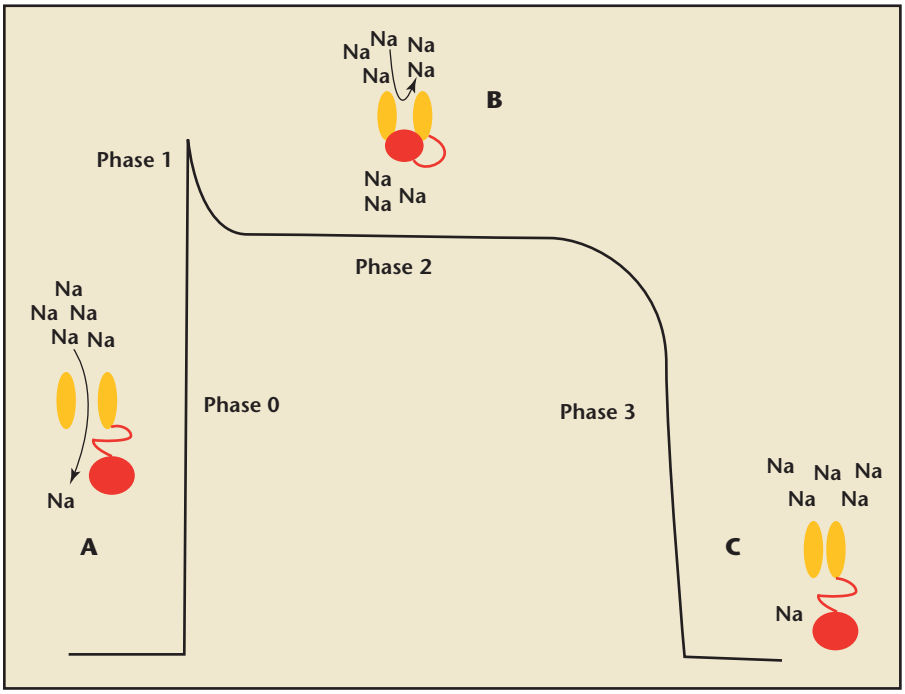
Na^+ Channel and Na^+ Currents

Cellular sodium influx is mediated by specific voltage-gated channels spanning the lipid bilayer of the cellular membrane. Upon reaching a critical transmembrane depolarization, sodium channels open, allowing sodium to flow along electrochemical gradients into the cell. Sodium channels are subsequently inactivated in 2 phases—fast and slow. Initial sodium influx results in phase 0 of the action potential, followed by rapid channel inactivation resulting in termination of further depolarization and the end of phase 0. The "late" sodium current occurs as a consequence of that small percentage of channels that do not immediately inactivate. These active, open channels allow continued sodium influx during the plateau phase of the action potential. Inactivated channels revert to a closed, active state upon repolarization of the cell membrane (Figure 1).

Pathologic conditions such as ischemia, hypoxia, presence of reactive oxygen species, SCN5A mutation, toxins, and heart failure potentiate the late sodium current through poorly understood mechanisms.[2] Late sodium current activity also varies between cardiac tissue, with greater activity in canine midmyocardial cells compared with epicardial and endocardial cells.[3] Although the magnitude of the late current is less than 1% than that of the peak current, intracellular sodium concentration is significantly increased with this current in the pathologic states described above.[4] Intracellular sodium accumulation leads to diastolic tonic contraction, depressed systolic function, and electrical instability in affected tissue via sodium-mediated calcium accumulation as described below. Electrical instability is further worsened by AP prolongation due to greater sodium influx during the plateau phase.

In nonpathologic states, the Na/Ca exchanger functions in the forward direction (influx of 3 Na^+ ions for efflux of 1 Ca^{2+} ion) during diastole

Figure 1. *During phase 0 upstroke, sodium ions flow through open, active channels* **(A)**. *Channels inactivate during phases 1 and 2. Ions cannot flow through inactive channels* **(B)**. *Upon repolarization, channels close and reactivate* **(C)**.



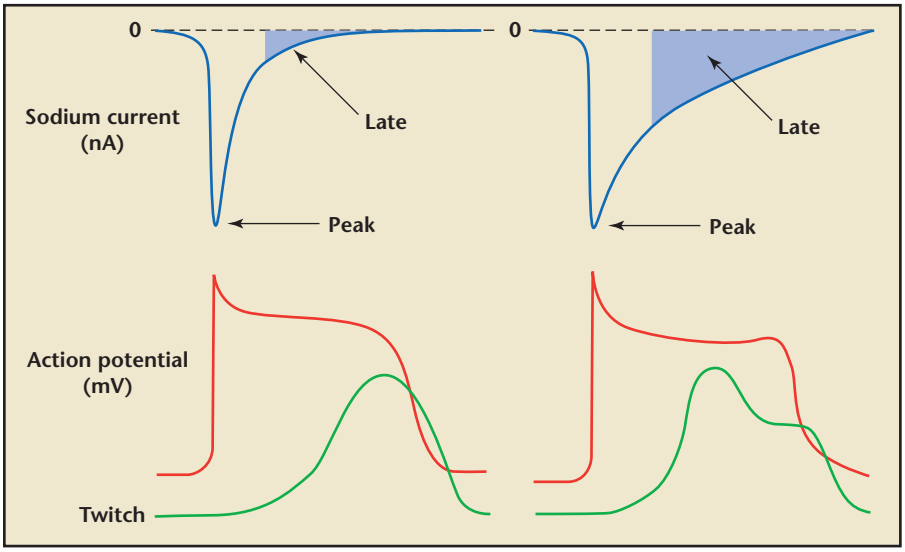


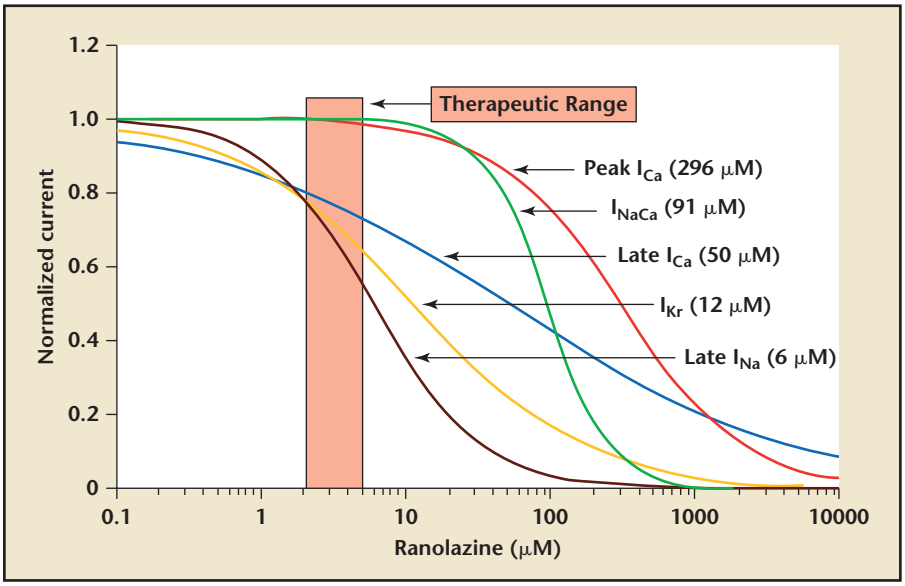
Figure 2. *Depiction of sodium currents in relation to action potential and muscle fiber twitch. A normal relationship is seen on the left. On the right, pathologically enhanced sodium current prolongs the action potential and leads to a significant tonic phase to fiber twitch. Reprinted from Belardinelli L et al. Inhibition of the late (sustained/persistent) sodium current: a potential drug target to reduce intracellular sodium-dependent calcium overload and its detrimental effects on cardiomyocyte function.* Eur Heart J Suppl. *2004;6(suppl I):13-17*[4] *with permission from Dr. Belardinelli and the European Society of Cardiology.*

and in reverse during the plateau phase of the AP. Increased intracellular Na and plateau phase duration favor reverse mode activity of the Na^+/Ca^{2+} exchanger, thus a natural consequence of the increased late sodium current is an overall increase of intracellular calcium. Mounting intracellular calcium accumulation results in increased diastolic tone, with concomitant increase in myocardial oxygen demand and decreased tension development during systole[4] (Figure 2). The mechanisms of such changes are beyond the scope of this review. However, calcium accumulation within myocardial cells may result in calcium-mediated calcium release from sarcoplasmic reticulum, delayed afterdepolarizations, and triggered activity. Prolongation of the AP results in transmural dispersion of refractoriness. Such states are classic conditions for arrhythmia generation. Inhibition of the late sodium current should reduce intracellular sodium-mediated calcium loading and prevent these adverse effects.

Electrophysiologic Effects of Ranolazine

The potential of ranolazine as an antiarrhythmic drug stems from observation of its ability to modify multiple ionic currents in cardiac cells responsible for generation of the action potential. Figure 3 illustrates the relative inhibitory effects of ranolazine at varying concentrations on cellular currents. At clinically meaningfully concentrations, inhibition of the late sodium current is profound. Inhibitory effects of I_{Kr} and I_{Ca} are also seen.[3] Although inhibition of depolarizing and repolarizing forces seems balanced, there is a modest QT prolongation resulting from treatment with ranolazine. Despite initial concerns about the potential that QT prolongation could lead to serious ventricular arrhythmias—as observed with other QT-prolonging drugs—ranolazine has been demonstrated not to increase arrhythmias, and, in fact, is antiarrhythmic. Ion current modulation in Purkinje and M-cells appears distinct from those of the epicardium. The complex channel blockade shortens AP duration in the M cells and Purkinje fibers while prolonging it in the epicardium.[3] The result is a

Figure 3. *Inhibitory effects of ranolazine at clinically relevant concentrations (2-6 μM/L) revealing selectivity for late sodium, I_{Kr}, and I_{Ca}. Numbers in parentheses are 50% inhibitory concentrations. Adapted with permission from Antzelevitch C et al.*[3]



reduction in dispersion of refractoriness across the ventricle with reduction in the potential for arrhythmia.

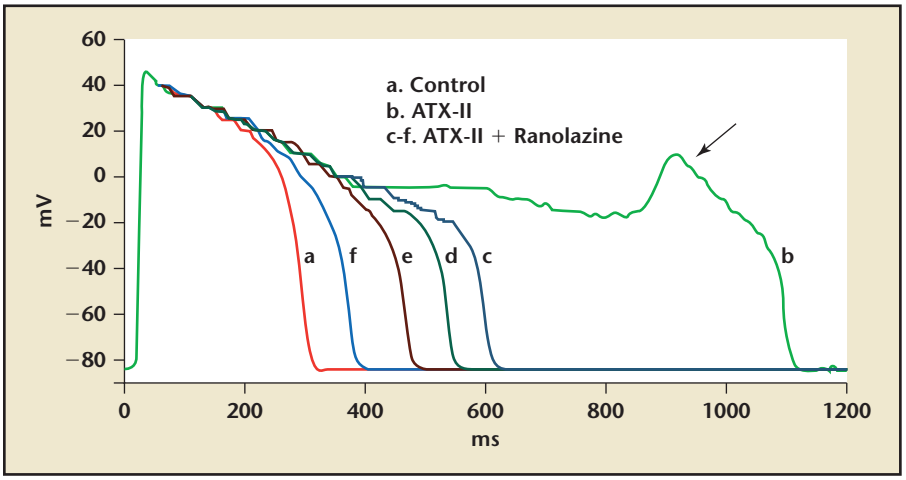
In an experimental model of failing canine ventricular myocytes, ranolazine was demonstrated to selectively and potently inhibit the late sodium current. Little effect was seen on the phase 0 upstroke due to such selectivity. In fact, ranolazine was 38 times more potent in inhibiting late versus peak sodium current in the canine model. Peak sodium current was inhibited at IC_{50} 244 μM compared with an IC_{50} of 6.5 μM for the late current.[5]

Potentiation of the late sodium current prolongs AP duration in pathologic states. Experimentally, late sodium current can be enhanced in vivo using sea anemone toxin (ATX-II). APs measured from isolated guinea pig ventricular myocytes displayed prolongation of AP duration and the development of EADs when exposed to ATX-II. Figure 4 illustrates the ability of ranolazine, in a concentration-dependent manner, to shorten AP duration and abate the occurrence of EADs. Furthermore, ranolazine normalized beat-to-beat AP duration variability in cells exposed to ATX-II.[6] Isolated atrial myocytes exposed to ATX-II developed EADs as well as delayed afterdepolarizations. Continued exposure resulted in regular triggered activity in those myocytes. Ranolazine abolished AP prolongation, afterdepolarizations, and triggered activity.[7] Protection from development of triggered activity in this model suggests a potential protective role against arrhythmia triggers in the clinical setting. Regulation of beat-to-beat AP duration results in less dispersion of refractoriness and may be an additional attractive characteristic of this drug.

Antiarrhythmic Observations With Ranolazine From the MERLIN-TIMI 36 Trial

Given its dramatic effect on the late sodium current, cellular calcium loading, and myocardial diastolic function, ranolazine was postulated to reduce myocardial oxygen demand and hence provide cardiac protection during acute ischemia. The Metabolic Efficiency with Ranolazine for Less Ischemia in Non–ST-Elevation Acute Coronary Syndromes–Thrombolysis In Myocardial Infarction 36 (MERLIN-TIMI 36) trial systematically examined outcomes of death, myocardial infarction, recurrent ischemia, and safety endpoints in non–ST-elevation acute coronary syndrome patients treated with ranolazine. Although found to be safe, ranolazine failed to reduce a composite outcome of cardiovascular death, myocardial infarction, and recurrent ischemia.[8] Subsequently, ambulatory electrocardiogram (ECG) monitor data from the MERLIN-TIMI 36 trial was examined to assess the arrhythmic or antiarrhythmic properties of ranolazine. Subjects in this trial wore ambulatory ECG monitors for 7 days after randomization. Although no differences in sustained ventricular tachyarrhythmia/ventricular fibrillation were noted in placebo versus active treatment, the overall incidence of such arrhythmia was rare, occurring in fewer than 1% of those studied. Otherwise, the antiarrhythmic effects of ranolazine were profound. The incidence of arrhythmia expressed as a percentage of the treatment or control group is demonstrated in Figure 5. Monomorphic ventricular tachyarrhythmia of less than 30 seconds' duration was significantly reduced from 8.3% in the control group to 5.3% in the active treatment group. Treatment with ranolazine trended toward protection against new-onset atrial fibrillation and significantly reduced sustained supraventricular tachyarrhythmia (55% of controls vs 44.7% of ranolazine). Of additional importance, ranolazine also protected against the occurrence of bradyarrhythmias and cardiac pauses.[9] These results are the strongest evidence of antiarrhythmic properties of ranolazine in humans. Although intriguing, such observations are far from conclusive and support only the need for further,

Figure 4. *Enhancement of the late sodium current with sea anemone toxin (ATX-II) prolongs action potential duration and leads to development of early afterdepolarizations. The addition of ranolazine at concentrations of 1, 3, 10, and 30 μmol/L shortens action potential duration and prevents development of early afterdepolarizations. Adapted with permission from Song Y et al.[6]*



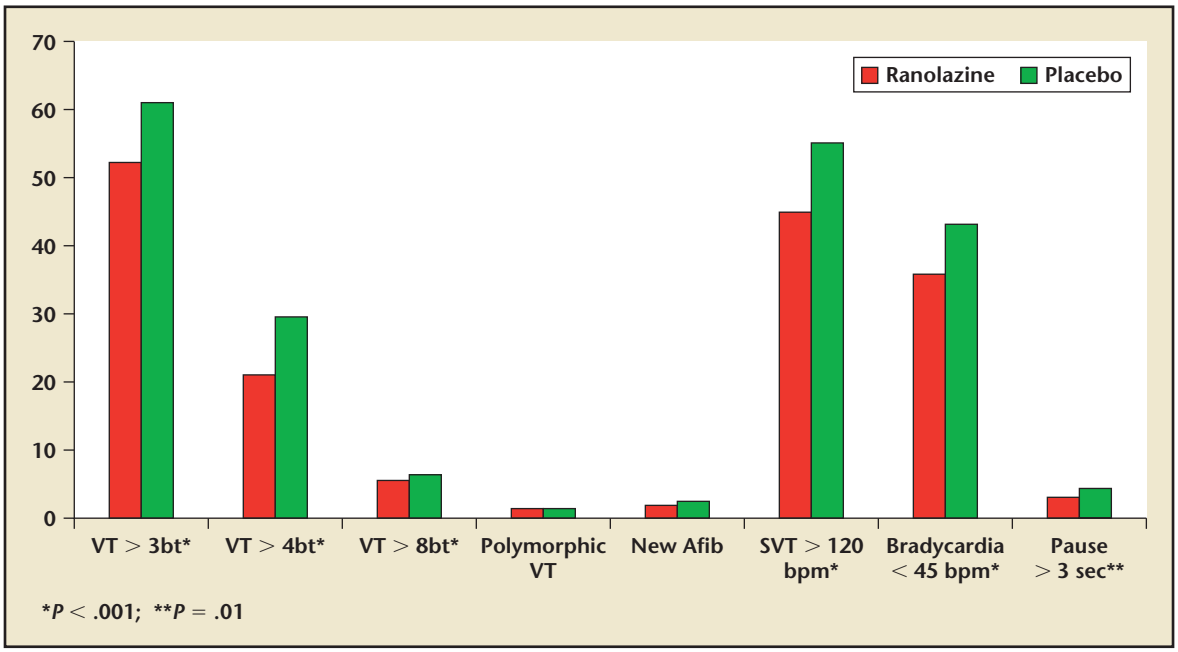


Figure 5. *Spontaneous arrhythmias observed during a 7-day Holter monitoring period in the MERLIN-TIMI 36 trial. Arrhythmia prevalence is expressed as a percentage of the total treatment group. Afib, atrial fibrillation; bpm, beats per minute; MERLIN-TIMI 36, Metabolic Efficiency with Ranolazine for Less Ischemia in Non–ST-Elevation Acute Coronary Syndromes–Thrombolysis In Myocardial Infarction 36; VT, ventricular tachycardia.*

specific study of these properties in well-designed human clinical trials.

Ranolazine as Suppressive Therapy for Atrial Fibrillation

Atrial fibrillation occurs in up to 1% of the population, with accrued annual heath care costs of more than $3000 per year.[10] Despite advances in radiofrequency ablation for treatment of atrial fibrillation, antiarrhythmic drugs remain one cornerstone of treatment. Currently available medications, such as amiodarone, sotalol, and class I antiarrhythmics, are limited with regard to efficacy, patient tolerance, and freedom from toxicity. Antiarrhythmic agents that have selective effects on atrial but not ventricular tissue may be advantageous for control of atrial arrhythmias, while minimizing ventricular proarrhythmia. Such atrial selectivity has been demonstrated with ranolazine in isolated canine myocytes. Ranolazine modified the contour of both atrial and ventricular APs in canine myocytes. In atrial cells, APs (APD_{90} and APD_{95}) were prolonged by 37 ms and 60 ms, respectively, versus baseline after treatment with ranolazine. In ventricular tissue, those same parameters were shortened by 23 ms and 25 ms.[11] Atrial effective refractory periods were prolonged in direct proportion to increasing concentrations of ranolazine. Additional post repolarization refractoriness was also seen. Furthermore, ranolazine slowed atrial conduction velocity by decreasing the slope phase 0 depolarization in a use-dependent manner. Uniquely in atrial tissue, it seems, there is less selectivity for the late sodium current over the peak sodium current responsible for depolarization during phase 0.

In canine perfused atrial preparations, exposure to acetylcholine resulted in sustained fibrillation. Atria were also induced to fibrillate after ischemia and reperfusion followed by exposure to isoproterenol. Ranolazine effectively suppressed development of atrial fibrillation in both experimental models.[11] Triggered activity within pulmonary veins has been postulated as a potential trigger for clinical atrial fibrillation. Additional experiments with isolated canine pulmonary vein sleeves yielded findings similar to those seen with perfused atrial preparations. Ranolazine effectively suppressed triggered activity elicited by isoproterenol and acetylcholine and significantly slowed phase 0 depolarization and conduction velocity in the canine pulmonary veins.[12]

Evidence supporting the utility of the drug against atrial fibrillation in humans is limited. One uncontrolled observational study of 7 patients who failed to maintain sinus rhythm despite treatment with other suppressive antiarrhythmic drugs supports the possibility of clinical

effectiveness for preventing recurrent atrial fibrillation. In these 7 patients, 4 patients remained in sinus rhythm and another initially responded but had recurrent atrial fibrillation at 3 months.[13] Although this study is limited in design and size, coupled with the findings from MERLIN-TIMI 36, it suggests the possibility that ranolazine may possess meaningful clinical activity against atrial fibrillation.

Ranolazine for Treatment of Long QT Syndrome

Long QT syndromes result from prolongation of ventricular AP duration, evidenced on surface ECG as prolongation of the QT interval. Patients are susceptible to potentially lethal arrhythmias, specifically, polymorphic ventricular tachycardia (torsades de pointes). Long QT syndrome 3 (LQT3) is caused by a mutation of the SCN5A gene encoding the sodium channel. The resultant gain-of-function enhances sodium current during the plateau phase of the cardiac action potential. Sodium influx increases secondary to rapid reactivation and reopening of individual sodium channels. Unlike the QT prolongation seen with ranolazine, the AP in this case prolongs to a greater degree in M cells over epicardial cells, an effect similar to that of I_{Kr} blocking antiarrhymics.[3] The result is an increased dispersion of refractoriness with an increase in susceptibility to re-entry and polymorphic ventricular tachycardia.

Wu and colleagues[14] elegantly demonstrated the effect of ranolazine on AP duration in a guinea pig model of LQT3. ATX-II emulates LQT3 by enhancing late sodium current, as previously discussed in this review. Chromanol 293B and E-4031 inhibit potassium currents I_{Ks} and I_{Kr}, respectively, and thus also lead to prolongation of the plateau phase and AP duration similar to other LQT variants. Ranolazine shortened the magnitude of AP prolongation associated with ATX treatment.[14] However, in preparations with AP prolongation due to E-4031, ranolazine did not reverse that effect, and no significant AP shortening was seen. Ranolazine only minimally increased the AP duration in the presence of chromanol 293B. These observations support the hypothesis that late sodium channel blockade by ranolazine is the factor responsible for AP duration shortening rather than I_K modulation.

Given that enhanced late sodium current is known to cause QT prolongation in LQT3, ranolazine is very attractive as a potential medical therapy for this life-threatening genetic condition. A small study of patients with the SCN5A-ΔKPQ mutation, resulting in type 3 LQT syndrome, described both the electrophysiologic and diastolic functional behavior after intravenous administration of ranolazine. During an 8-hour infusion, ranolazine significantly shortened the mean surface QT interval from 576 ms ± 94 ms to 544 ms ± 100 ms and the QTc from 548 ± 53 to 526 ± 53. Q to T_{peak} was also significantly shortened.[15] Interestingly, a rebound phenomenon was observed whereby the QT parameters lengthened beyond the baseline measurements after discontinuation of infusion. Although intriguing, this evidence is inadequate to, and not intended to, support clinical use of ranolazine in the treatment of LQT3 syndrome. Further investigation, especially into the suppression of ventricular tachycardia, is necessary before the drug can be adapted to clinical practice for LQT3. Large clinical trials will be challenging to accomplish in the LQT3 patients given the relative rarity of this condition and heterogeneity of individual channel mutations, but it is hoped that the carefully controlled pilot trials that are underway will offer insight as to whether ranolazine is a viable therapy to pursue in selected patients.

Ranolazine and Sinus Node Dysfunction

Sinus node dysfunction, or sick sinus syndrome (SSS), is a condition that afflicts as many as 1 in 600 patients older than 65.[16] The symptoms associated with SSS include syncope, presyncope, fatigue, decreased exertional tolerance, dyspnea, and mental status changes. Patients with SSS may have underlying coronary artery disease and exacerbation of their bradyarrhythmia with β-blocker therapy (an important therapy for prevention of sudden cardiac arrest and recurrent myocardial infarction). Standard treatment of SSS is implantation of atrial or dual-chamber pacemakers. Aside from withdrawal of bradycardic drugs, no medical therapy for SSS exists.[17] Of interest, in the MERLIN-TIMI 36 trial, bradycardia improved significantly[9] (Figure 5). Based on these clinical observations, the hypothesis that ranolazine can be used to treat symptomatic bradycardia in sinus node dysfunction has been proposed.

The mechanism of mitigation of bradyarrhythmias by ranolazine is unproven at this time. It has been demonstrated that the sodium channel (SCN5A) participates as a depolarizing current in the sinus node.[18] The late sodium current will result in block of the depolarizing sodium current by delaying voltage-dependent sodium channel inactivation. This phenomenon has been demonstrated with in vitro testing of 1795insD mutant Na^+ channels that account for one of the LST3

genotypes.[19] In experimental models, blockade of late sodium current with ranolazine has been demonstrated to improve the depolarizing sodium current and increase heart rate.[20] Thus, ranolazine could be a potent antiarrhythmic drug for the tachybrady syndrome, with effective atrial fibrillation suppression and augmentation of sinus bradycardia.

Summary

In stark contrast to currently available antiarrhythmic drugs, ranolazine is well tolerated and has few side effects. The electrophysiological properties of the drug described in this article are intriguing. Ranolazine possesses strong use-dependent sodium current antagonist properties, with unique affinities between the atria and ventricle. Additionally, ranolazine inhibits potassium currents in a pattern distinct from traditional class III antiarrhythmics, thus avoiding potentially proarrhythmic side effects. Small clinical trials are encouraging but, at this time, they support only the need for further rigorous prospective randomized testing of ranolazine as a therapeutic option for cardiac rhythm disorders. Currently, clinical data are limited to the results of MERLIN-TIMI 36 and small-scale human trials.[9,13,15] Should the science described within this article translate to clinically relevant arrhythmia protection, ranolazine may become an invaluable treatment option. ■

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Main Points

- Cellular sodium influx is mediated by specific voltage-gated channels spanning the lipid bilayer of the cellular membrane.
- Pathologic conditions such as ischemia, hypoxia, presence of reactive oxygen species, SCN5A mutation, toxins, and heart failure potentiate the late sodium current through poorly understood mechanisms.
- Calcium accumulation within myocardial cells may result in calcium-mediated calcium release from sarcoplasmic reticulum, delayed afterdepolarizations, and triggered activity.
- Inhibition of the late sodium current should reduce intracellular sodium-mediated calcium loading and prevent adverse effects.
- The potential of ranolazine as an antiarrhythmic drug stems from observation of its ability to modify multiple ionic currents in cardiac cells responsible for generation of the action potential.
- In the Metabolic Efficiency with Ranolazine for Less Ischemia in Non–ST-Elevation Acute Coronary Syndromes–Thrombolysis In Myocardial Infarction 36 (MERLIN-TIMI 36) trial, treatment with ranolazine trended toward protection against new onset atrial fibrillation and significantly reduced sustained supraventricular tachyarrhythmia.

Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation*. 2006;114:e257-e354.
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