Antiarrhythmic Effects of Ranolazine in a Guinea Pig in Vitro Model of Long-QT Syndrome

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ABSTRACT

Prolongation of the QT interval of the ECG is associated with increased risk of torsades de pointes ventricular tachycardia. Ranolazine, a novel antianginal agent, is reported to decrease the delayed rectifier potassium current, I_{Kr}, and to increase action potential duration (APD) and the QT interval. However, ranolazine is also reported to reduce late sodium current (late INa), a depolarizing current that contributes to prolongation of the plateau of the ventricular action potential. We hypothesized that ranolazine would decrease APD and the occurrence of arrhythmias when late INa is increased. Therefore, we measured the effects of ranolazine alone and in the presence of anemone toxin (ATX)-II, whose action mimics the sodium channelopathy associated with long-QT3 syndrome, on epicardial monophasic action potentials and ECGs recorded from guinea pig isolated hearts. Ranolazine (0.1–50 μM) prolonged monophasic APD at 90% repolarization (MAPD_{90}) by up to 22% but did not cause either early afterdepolarizations (EADs) or ventricular tachycardia (VT), ATX-II (1–20 nM) markedly increased APD and caused EADs and VT. Ranolazine (5–30 μM) significantly attenuated increases in MAPD_{90} and reduced episodes of EADs and VT produced by ATX-II. Ranolazine also attenuated the synergistic effect of MAPD_{90} increase caused by combinations of ATX-II and blockers of I_{Kr} [E-4031; 1-(2-(6-methyl-2-pyridyl)ethyl]-4-methylsulfonylaminobenzoyl)piperidine]. Thus, although ranolazine alone prolonged APD, it reduced APD and ventricular arrhythmias caused by agents that increased late INa and decreased I_{Kr}.

Prolongation of the duration of the ventricular action potential (indicated on the surface electrocardiogram as an increase of the QT interval) due to inhibition of the rapid delayed-rectifier potassium current, I_{Kr}, is caused by drugs from many therapeutic classes and is associated with an increased risk of ventricular tachyarrhythmias such as torsades de pointes (TdP) (Belardinelli et al., 2003). However, QT interval prolongation per se may not be proarrhythmic (Hondeghem et al., 2001). Ranolazine is a novel antianginal drug (Peippe and Wolff, 1999; Louis et al., 2002; Chaitman et al., 2004), and it prolongs the QT interval but is not known to increase the incidence of ventricular tachycardias (VTs) and may reduce the incidence of ischemia-related arrhythmias (Gralinski et al., 1996). At a cellular level, ranolazine has been found to reduce the peak outward current conducted by the delayed rectifier potassium channel I_{Kr} with a potency (IC_{50} value) of 11.5 μM (Zygmunt et al., 2002) and to reduce the late inward sodium current (late INa) with an IC_{50} of 5 to 21 μM, depending on pacing frequency and membrane potential (Zygmunt et al., 2002; Song et al., 2004).

Inhibitions of I_{Kr} and late INa by ranolazine would be expected to have opposite effects on the duration of the QT interval. Whereas inhibition of I_{Kr} prolongs action potential duration (APD), inhibition of late INa decreases APD. Thus, the effect of ranolazine on the QT interval may depend on the relative magnitudes of ranolazine-induced changes in I_{Kr} and late INa and the contributions of these ion currents to ventricular repolarization. We speculated that ranolazine may be useful to reduce the QT interval and the incidence of early afterdepolarizations (EADs) and TdP when late INa is elevated, as in heritable and/or acquired forms of the long-QT3 (LQT3) syndrome. To test this hypothesis, the electrophysiological effects of ranolazine on the ventricle of the guinea pig isolated heart were determined in the absence and presence of agents that increase late INa and/or decrease repolarizing potassium currents, thereby prolonging the durations of the ventricular action potential and the QT interval. To increase late INa hearts were exposed to Anemonia sulcata toxin (ATX)-II. ATX-II prevents full inactivation of the inward sodium current (Isenberg and Ravens, 1984) and therefore

Abbreviations: TdP, torsades de pointes; VT, ventricular tachycardia; APD, action potential duration; EAD, early afterdepolarization; LQT3, long QT syndrome 3; ATX, anemone toxin; A-V, atrioventricular; CPA, N^6-cyclopentyladenosine; MAPD, monophasic action potential duration; MAP, monophasic action potential.
mimics in exaggerated manner mutations of the cardiac sodium channel gene SCN5A that are implicated as the mechanism for the LQT3 form of long-QT syndrome (Bennett et al., 1995; Wang et al., 1995; Priori et al., 1996). Two drugs that are reported to mimic forms 1 and 2 of the long-QT syndrome were used to further prolong the duration of the ventricular action potential in the presence of low concentrations of ATX-II: chromanol 293B (LQT1) and E-4031 (LQT2). Chromanol 293B is a relatively selective blocker of IKs (Sun et al., 2001), the slowly-activating delayed-rectifier potassium current (Barhanin et al., 1996). Mutations in the gene KCNQ1 (KcLQT1) may result in a decrease of IKs, prolongation of action potential duration, and the LQT1 form of long-QT syndrome (Shalaby et al., 1997). E-4031 was shown (Sanguinetti and Jurkiewicz, 1990) to decrease the rapidly activating potassium current IKr, a change that mimics the effect of unfavorable mutations of the potassium channel gene KCNJ2 (HERG) that are the molecular mechanism of LQT2 (Curran et al., 1995). Class III antiarrhythmic drugs, female gender, hypokalemia, and electrical remodeling in cardiac hypertrophy and failure may reduce the magnitude of repolarizing potassium currents and increase the risk of TdP (Vos et al., 2001; Marban, 2002). In addition, late INa seems to be increased in left ventricular myocytes from failing hearts (Undrovinas et al., 2002). Regardless, ATX-II in combination with either the IKr blocker E-4031 or the IKr blocker chromanol 293B were used in the present study to mimic concurrent channelopathies (Marban, 2002) that may be present in clinical situations in which antiarrhythmic drugs are used. The guinea pig isolated heart was used in this study because both IKr and IKs are present in guinea pig, as in human, ventricular myocytes (Zicha et al., 2003).

Materials and Methods

Animal Model. Hartley guinea pigs of both sexes and weighing 250 to 300 g were purchased from Simonsen Laboratories (Gilroy, CA). Animal use in this study was reviewed and approved by the Institutional Animal Care and Use Committee of CV Therapeutics, Inc. (Palo Alto, CA). Animals were anesthetized with isoflurane. Hearts were excised and perfused by the Langendorff method at 10 °C with Krebs-Henseleit solution (118 mM NaCl, 2.5 mM KCl, 1.2 mM KH₂PO₄, 2.5 mM CaCl₂, 0.5 mM MgSO₄, 2.0 mM pyruvate, 5.5 mM glucose, 0.57 mM Na₂EDTA, and 25 mM NaHCO₃, pH adjusted to 7.4) warmed to 33°C. Isoflurane was chosen as the anesthetic agent because it does not seem to inhibit the induction of TdP or to reduce the transmural dispersion of repolarization in the ventricle, and it may actually facilitate these phenomena (Antzelevitch et al., 1999). To facilitate exit of fluid from the left ventricle, the leaflets of the mitral valve were trimmed with fine scissors. The right atrial wall was partially removed and a bipolar Teflon-coated electrode was placed on the right ventricular free wall. One end of a Teflon-coated tungsten unipolar electrode was inserted in the middle of the sponge and the opposite end plugged into the input of an ECG amplifier. The reference electrode was placed directly into the ventricular epicardial wall close to the A-V valves. ECG, MAP, and coronary perfusion pressure signals were collected in real time and stored on a computer for subsequent analysis.

To record an ECG, a 1-cm thick sponge ring soaked in saline was placed on the right ventricular free wall. One end of a Teflon-coated tungsten unipolar electrode was inserted in the middle of the sponge and the opposite end plugged into the input of an ECG amplifier. The reference electrode was placed directly into the ventricular epicardial wall close to the A-V valves. ECG, MAP, and coronary perfusion pressure signals were collected in real time and stored on a computer for subsequent analysis.

Drug Concentration-Response Relationships. Increasing concentrations of drug were infused in a cumulative manner, allowing 7 to 15 min between changes of concentration. To investigate the rate dependence of effects of drugs on the duration of the ventricular MAP, the ventricular pacing rate was increased stepwise from 1 to 1.5, 2, and 2.5 Hz. Each pacing rate was maintained for 2 min, and MAPs were measured during the last 5 s of each period. The pacing rate was then reduced to 1 Hz, and a 15-min infusion of either ATX-II (7 nM), chromanol 293B (1 μM), E-3041 (1 μM), or ranolazine (5 μM) was begun. When MAPD₉₀ prolongation attained an apparent steady state in the presence of drugs, the ventricular pacing rate was again increased progressively, and MAPs were recorded.

Determination of Antiarrhythmic Effects of Ranolazine. VT was defined as a sequence of three or more ventricular depolarizations at a rate >1.5 Hz. VT that terminated spontaneously was defined as transient or non sustained VT. VT that did not subside spontaneously unless interrupted by an antitachycardia treatment (ranolazine) was defined as sustained VT. Polymorphic VT (TdP-like VT) was defined as VT with much faster rate and different morphology in both MAP and ECG recordings. A positive depolarization during phase 2 and/or 3 of an action potential was defined as an EAD when associated with T wave changes on ECG recording and as a ventricular extrasystolic beat when associated with a QRS complex in the ECG. Confirmation of the spontaneous origin of VT was obtained by its persistence and recurrence when delivery of pacing stimuli was suspended for a minimum of 10 s.

Statistical Analysis. All data are reported as means ± S.E.M. Concentration-response curves were analyzed using Prism version 3.0 (GraphPad Software Inc., San Diego, CA). Repeated measure one-way analysis of variance was used to compare values of measurements obtained from the same heart before and after treatment. When analysis of variance revealed the existence of a significant difference among values, the Student-Newman-Keuls test was applied to determine the significance of a difference between a selected pair of group means. A p value <0.05 was taken as an upper limit to indicate a significant difference.

Sources of Drugs. Ranolazine [ranexa, (±)-N-(2,6-dimethyl-phenyl)-(4-hydroxy-3-(2-methoxyphenoxy)propyl]-1-piperazine] was synthesized at CV Therapeutics, Inc. CPA were purchased from Sigma-Aldrich (St. Louis, MO), ATX-II and E-4031 (1-[2-(6-methyl-2-pyridyl)ethyl]-4-methylsulfonylaminobenzoyl)-
Effects of ATX-II, Chromanol 293B, E-4031, and Ranolazine on MAPD$_{90}$, EADs, and Arrhythmias. ATX-II, E-4031, chromanol 293B, and ranolazine each increased the duration of the MAP recorded from the guinea pig heart in a concentration-dependent manner (Fig. 1). E-4031 (10 μM), chromanol 293B (10 μM), and ranolazine (50 μM) increased the duration of the MAP by 50 ± 4% (n = 9), 12 ± 3% (n = 9), and 22 ± 2% (n = 13), respectively (Fig. 1). The maximum effect of ATX-II on MAPD$_{90}$ could not be determined because ATX-II (>20 nM) caused frequent premature ventricular beats or sustained episodes of VT that interfered with the calculation of MAPD$_{90}$. High concentrations (1–10 μM) of E-4031 also caused EADs that did not progress to VT in the six hearts studied. Chromanol 293B and ranolazine each caused a moderate prolongation of MAPD$_{90}$, but did not cause either EADs or VT (Fig. 1).

Attenuation by Ranolazine of the Effect of ATX-II on MAPD$_{90}$. The concentration-response relationship for ATX-II to increase the duration of the MAP was significantly flattened by 5 μM ranolazine (Fig. 2). Ranolazine (5 μM) alone produced a sustained, small (16% above baseline) prolongation of MAPD$_{90}$ from 202 ± 9 to 235 ± 4 ms (n = 7), but this prolongation was not additive to that caused by ATX-II. In contrast, the action of ATX-II to lengthen MAPD$_{90}$ was markedly reduced by ranolazine (Figs. 2 and 3). An example of a record from one of seven hearts exposed to ranolazine in the presence of ATX-II is shown in Fig. 3.

Attenuation by Ranolazine of ATX-II-Induced EADs and VT. Ranolazine greatly reduced the occurrence of EADs, frequent premature ventricular beats, and VT caused by ATX-II. Representative experimental recordings from two of 13 hearts perfused with solution containing 20 nM ATX-II are shown in Fig. 4. Perfusion of hearts with 20 nM ATX-II for 15 min led to significant prolongation of the MAPD and the QT interval, EADs, and ventricular extrasystolic beats, which were followed by episodes of transient and sustained polymorphic VT (Fig. 4, A and B) in all hearts. These rhythm abnormalities were not observed under control conditions in the absence of ATX-II. Administration of 5 to 10 μM ranolazine in the continued presence of 20 nM ATX-II led to the suppression of EADs, abolishment of polymorphic VTs, and restoration of a regular ventricular response to pacing (Fig. 4B, record c). EADs and polymorphic VT reappeared after termination of ranolazine infusion (Fig. 4B, record d). Thus, ranolazine reversibly terminated polymorphic or polymorphic (EAD-triggered) VT caused by ATX-II (20 nM).

Ranolazine not only reversed but also prevented the appearance of EADs, frequent premature ventricular beats, and VT caused by ATX-II. In experiments wherein hearts (n = 7; Fig. 2) were pre-treated with 5 μM ranolazine, no EADs or VTs were observed when hearts were subsequently exposed to concentrations of ATX-II as high as 100 nM in the continued presence of ranolazine.

Antagonism by Ranolazine of the MAPD$_{90}$ Prolongation Caused by ATX-II Plus E-4031 and Chromanol 293B. Ranolazine attenuated the actions of combinations of ATX-II with E-4031 (Fig. 5, A and B) and chromanol 293B (not shown). In hearts paced at 1.5 Hz, perfusion of a low concentration of either ATX-II (7 nM) or E-4031 (1 μM) produced moderate prolongations of MAPD$_{90}$ (71 ± 8 and 61 ± 9 ms; n = 3 and 4, respectively) (Fig. 5B). Perfusion of ATX-II (7 nM) plus E-4031 (1 μM) produced a marked synergistic increase of MAPD$_{90}$ by 325 ± 107 ms (Fig. 5B). Ranolazine (5, 10, and 30 μM) significantly attenuated the effects of ATX-II plus E-4031 to prolong MAPD$_{90}$ (Fig. 5B). Similarly, ranolazine significantly (p < 0.05; n = 4) attenuated the prolongation of MAPD$_{90}$ caused by a combination of 7 nM ATX-II and 1 μM chromanol 293B. In hearts (n = 4) perfused with chromanol 293B (1 μM) alone or in combina-
tion with ATX-II (7 nM), MAPD₉₀ was prolonged by 12 ± 4 and 68 ± 3 ms, respectively, above control. In the continued presence of 1 μM chromanol 293B and 7 nM ATX-II, ranolazine (5, 10, and 30 μM) reduced the prolongation of MAPD₉₀ from 68 ± 3 to 53 ± 3, 45 ± 3, and 38 ± 5 ms, respectively (n = 4; P < 0.05). Interestingly, ranolazine neither increased nor decreased MAPD₉₀ in the presence of E-4031 alone (i.e., in the absence of ATX-II). E-4031 (1 μM) increased MAPD₉₀ by 54 ± 9 ms from 211 ± 9 (control) to 265 ± 9 ms (n = 5; p < 0.05). Values of MAPD₉₀ in the presence of 1 μM E-4031 with 5, 10, and 30 μM ranolazine were 267 ± 10, 266 ± 11, and 263 ± 14 ms, respectively (n = 5; p > 0.05 versus E-4031 alone). In contrast, ranolazine increased MAPD₉₀ in the presence of the Iᵥ blocker chromanol 293B. Chromanol 293B (1 μM) increased MAPD₉₀ by 14 ± 6 (n = 5) ms above control. Values of MAPD₉₀ in the presence of chromanol 293B alone and with 5, 10, and 30 μM ranolazine were 208 ± 4, 220 ± 5, 224 ± 6, and 240 ± 6 ms, respectively (n = 5; p < 0.01 for 30 μM ranolazine versus chromanol 293B alone).

**Lack of Rate Dependence of Action of Ranolazine on Duration of the MAP.** Antiarrhythmic drugs must be effective at high heart rates; therefore, knowledge of the dependence of drug action on heart rate is useful to predict efficacy of a prospective antiarrhythmic agent (Hondeghem and Snyder, 1990). Reverse use dependence is considered to be a proarrhythmic risk factor. The effect of a decrease in pacing cycle length (increase of pacing frequency) on prolongations of MAPD₉₀ by ranolazine, ATX-II, E-4031, and chromanol 293B is shown in Fig. 6. As expected, duration of the MAP decreased with a decrease in pacing cycle length in control.

Fig. 4. Representative records showing effects of ATX-II and ranolazine on guinea pig left ventricular MAPs and ECGs. A, MAP and ECG signals recorded sequentially from a single heart in the absence of drug (a) and in the presence of 20 nM ATX-II (b and c) and 20 nM ATX-II plus 10 μM ranolazine (d). EADs in MAP signals corresponded to T wave changes in ECG without (b) or with (c) triggered extra ventricular beats. B, records of MAP and ECG signals depicting the effect of ranolazine to terminate ATX-II-induced polymorphic VT. MAP (top) and ECG (bottom) signals were recorded sequentially from a guinea pig heart in the absence (a) and presence of drugs as indicated (b–d) in each of the four panels.
hearts (Fig. 6, left). Ranolazine and chromanol 293B did not alter this relationship, whereas E-4031 and ATX-II steepened it (Fig. 6, left). This is shown more clearly in Fig. 6, right, where the differences in values of MAPD<sub>90</sub> between drug-treated and control hearts are plotted as a function of pacing cycle length. An absence of rate dependence is indicated by a zero slope of the relationship between cycle length and MAPD<sub>90</sub> (i.e., a line parallel to the abscissa). Prolongations of MAPD<sub>90</sub> caused either by ranolazine or by the I<sub>Kr</sub> blocker chromanol 293B were independent of rate, with slope values that were not significantly different from zero. On the other hand, the frequency-response plots describing the effects of E-4031 and ATX-II on MAPD<sub>90</sub> had significantly positive slopes (0.018 ± 0.003 and 0.026 ± 0.07, respectively), indicative of a reverse rate dependence of the effects of E-4031 and ATX-II.

**Discussion**

Drug-induced reduction of I<sub>Kr</sub>, prolongation of the QT interval, and TdP are a potential risk during treatment with a wide range of drugs from diverse therapeutic classes (Hondeghem et al., 2001; Belardinelli et al., 2003). Therefore, we sought to determine whether the APD prolongation caused by ranolazine was associated with proarrhythmic activity. In keeping with its effect to reduce outward potassium current (I<sub>Kr</sub> blockade), ranolazine prolonged left ventricle MAPD<sub>90</sub>. However, as now acknowledged by many investigators, some drugs that prolong the duration of the ventricular action potential and the QT interval do not increase the risk of TdP (Hondeghem et al., 2001; Studenik et al., 2001; van Opstal et al., 2001). Thus, of particular interest are the results that 1) ranolazine alone did not cause EADs, ectopic beats, and VT; 2) ranolazine markedly reduced the proarrhythmic effects of ATX-II (Figs. 2–4); and 3) ranolazine reduced the duration of the MAP in the presence of a combination of two agents (ATX-II and E-4031) that act by different mechanisms to increase MAPD<sub>90</sub> (Fig. 5). The mechanism by which ranolazine decreased APD in the presence of ATX-II and 1 μM E-4031 (Fig. 5) is likely to be a reduction of late I<sub>Na</sub>. Because ranolazine decreased ventricular MAPD in the presence of combinations of ATX-II with either E-4031 or chromanol 293B, but not in the presence of the I<sub>Kr</sub> blockers alone (i.e., absence of ATX-II), the data suggest that ranolazine is effective to reduce MAPD only when late I<sub>Na</sub> contributes significantly to prolongation of the action potential. However, it is also possible that ranolazine and E-4031 compete for the same binding site in the HERG channel, because both ranolazine and E-4031 inhibit I<sub>Kr</sub>. The result that ranolazine markedly reduced prolongation of the MAP caused by ATX-II supports the findings by Zygmunt et al. (2002) and Song et al. (2004) that ranolazine decreased late I<sub>Na</sub>.

**Fig. 5.** Effect of ranolazine to attenuate prolongation of the ventricular monophasic action potential caused by the combination of ATX-II and E-4031. A, MAP recorded from an isolated guinea pig heart. Numbers indicate the sequence in which hearts were exposed to drugs. B, summary of effects of ATX-II (A; 7 nM, n = 3) and E-4031 (E; 1 μM, n = 4) alone and in combination (n = 7) and in the presence of ranolazine (R; n = 7). An * indicates a significant difference from A + E, p < 0.001.

**Fig. 6.** Rate dependence of actions of ranolazine, E-4031, ATX-II, and chromanol 293B on the duration of the ventricular MAPD<sub>90</sub> in guinea pig isolated heart. Left, relationship of MAPD<sub>90</sub> to pacing cycle length during the absence (control) and presence of either ranolazine (n = 5), E-4031 (n = 6), ATX-II (n = 6), or chromanol 293B (n = 5). Right, values of MAPD<sub>90</sub> at different pacing cycle lengths using data shown in the left panel, with drug effects expressed as differences from control responses obtained in the same heart.
thus increasing both the inward current entering the cardiomyocyte during the plateau of the action potential, and action potential duration. This “gain of function” by the sodium channel delays repolarization and facilitates the development of EADs (Isenberg and Ravens, 1984; Studenik et al., 2001). The actions of ATX-II resemble those caused by mutations in the gene SCN5A (Bennett et al., 1995; Wang et al., 1995) that lead to repeated openings of sodium channels during the action potential plateau. Thus, the guinea pig isolated heart exposed to ATX-II is a model for the human LQT3 syndrome, which is characterized by a long QT interval and increased susceptibility to TdP induced by drugs that reduce outward currents during the action potential plateau, namely, blockers of I Kr (Makita et al., 2002). Patients with LQT3 syndrome are at increased risk of TdP (Rodén, 2000; Schwartz et al., 2001). In hearts pretreated with ATX-II, ranolazine not only did not further prolong, but in contrast, shortened the duration of the MAP. Thus, it seems that the action of ranolazine to inhibit late I Na has more effect on action potential duration than its action to block I Kr under conditions that cause an increase of late I Na.

A recent report of the effects of ranolazine to attenuate ATX-II-induced increases of late I Na and EADs in guinea pig isolated ventricular myocytes (Song et al., 2004) is consistent with the results shown in the present study. Thus, it is likely that the afterdepolarizations caused by ATX-II (and abolished by ranolazine) noted in recordings of MAP in this study (Fig. 4A) are indicative of the presence of EADs, as we have concluded. The effects of ranolazine to reduce late I Na, ventricular arrhythmias and prolongation of the MAP in the presence of ATX-II are similar to those of mexiletine, a class IB antiarrhythmic agent (sodium channel blocker) (Shimizu and Antzelevich, 1997). Mexiletine was found to have a greater effect to block SCN5A mutant sodium channels than to block wild-type sodium channels (Wang et al., 1997).

Increased late I Na and reductions in repolarizing K+ currents, whether caused by drugs or by heritable ion channel dysfunction, prolong the QT interval, and are major predisposing factors for TdP in humans (Sasyniuk et al., 1989). Prolongation of the QT interval beyond a certain limit may herald proarrhythmic episodes (Shaffer et al., 2002). If life-threatening ventricular tachycardia episodes are almost invariably the consequence of a considerably prolonged QT interval, then a drug like ranolazine with the property of limiting or reducing drug or disease-induced prolongation of the QT interval may be of therapeutic value. However, much additional research is required before the present results can be extrapolated to clinical practice. The temporal and spatial patterns of electrical activity, ion channel expression, and physiological/pathological regulation of ion channel function of the human heart ventricle are not fully replicated in hearts of animals used for experimentation. In particular, as regards the present study, the potassium currents of guinea pig ventricular myocytes differ in relative magnitude from those of human ventricular myocytes; the magnitude of I Kr is less, whereas the magnitude of I Na is greater in the guinea pig compared with the human ventricular myocyte (Zicha et al., 2003).

In contrast to classical class III antiarrhythmic agents and E-4031, which block I Kr, ranolazine prolonged cardiac repolarization in a way that did not wane when pacing rate was increased. Ideally, ventricular tachycardias would be treated with an antiarrhythmic agent whose effectiveness rose as heart rate increased (Hongdeghem and Snyder, 1990). Unfortunately, many class III antiarrhythmic agents are less effective in prolonging action potential duration at high than at low heart rates (Hongdeghem and Snyder, 1990).

In conclusion, the results of this investigation indicate that the prolongation of action potential duration by ranolazine seems not to be associated with an increased probability of ventricular arrhythmias (EADs or VT). This finding lends credence to the proposal that prolongation of action potential duration per se is not proarrhythmic. Ranolazine reduced the prolongation of cardiac repolarization caused by drugs that mimic ion channelopathies associated with increased late I Na or decreased I Kr and terminated episodes of ATX-II–induced nonsustained and sustained ventricular tachycardia. The prolongation of MAPD caused by ranolazine was independent of ventricular rate. Thus, under circumstances where late I Na is increased, ranolazine seems to act as an antiarrhythmic drug.

References
Hongdeghem LM and Snyder DS (1997) Class III antiarrhythmic agents have a lot of potential but a long way to go. Reduced effectiveness and dangers of reverse use dependence. Circulation 81:686–690.


Shimizu W and Antzelevitch C (1997) Sodium channel block with mexiletine is effective in reducing dispersion of repolarization and preventing torsade de pointes in LQT2 and LQT3 models of the long-QT syndrome. *Circulation* 96:2038–2047.


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