Is ranolazine an antiarrhythmic drug?

Lee L. Eckhardt, Tom C. Teelin, and Craig T. January

Division of Cardiovascular Medicine, Department of Medicine, University of Wisconsin-Madison, Madison, Wisconsin

Ranolazine is a new therapeutic agent clinically indicated for symptomatic relief of chronic angina pectoris for individuals already taking standard antianginal therapy. It has been shown to reduce the frequency of anginal episodes and increase exercise tolerance (5, 6, 22). The mechanism of the antianginal effects of ranolazine are uncertain but may be related to its ability to inhibit late Na⁺ current (I_{Na}^L) (1, 21). Beyond its antianginal effects, some preclinical studies have suggested that ranolazine may also have antiarrhythmic potential. In their article, Song et al. (20a) build on their previous investigations with ranolazine and its potential for antiarrhythmic activity.

Is ranolazine antiarrhythmic? In the first part of the article, these authors (20a) recapitulate findings in previous work with ranolazine. With the application of ATX-II, a sea anemone toxin known to increase late Na⁺ current (I_{Na}^L) (1, 21), to guinea pig atrial myocytes, these authors show action potential lengthening followed by early afterdepolarization (EAD) generation, then delayed afterdepolarization (DAD) generation, and finally DAD-initiated triggered action potentials with the disappearance of EADs. These effects of ATX-II on action potentials were nearly completely reversed with the application of a near therapeutic concentration of ranolazine (10 μM; therapeutic being 2–6 μM; Ref. 1), as well as tetrodotoxin (TTX), and in voltage-clamp studies, these suppressed ATX-II increased late I_{Na}^L. A new finding the authors show is that ranolazine, as well as TTX, can also suppress ATX-II-induced transient inward current (I_{TII}). I_{TII} is a Ca²⁺-dependent transient inward current thought to be driven by extracellular Na⁺/Ca²⁺ exchange, Ca²⁺-activated nonselective cation channels, and possibly Ca²⁺-activated chloride channels, and it is the depolarizing current associated with DADs (9). The authors propose that increased late I_{Na}^L results in intracellular Na⁺ loading, which via Na⁺/Ca²⁺ exchange increases intracellular Ca²⁺ concentration to lead to Ca²⁺-overload-induced cyclical Ca²⁺ release from the sarcoplasmic reticulum (SR). They then performed additional experiments with their ATX-II action potential model to show that suppression of Na⁺/Ca²⁺ exchange (by KB-R7943) or SR Ca²⁺ release (by ryanodine), or buffering directly cell Ca²⁺ (with EGTA or BAPTA)-suppressed DAD but not EAD generation. There was no attempt to quantify intracellular Na⁺ or Ca²⁺ in these experiments. Overall, the findings show suppression of DADs, DAD-triggered activity, and EADs in a putative Na⁺- and Ca²⁺-overload atrial myocyte model of arrhythmogenesis.

Ranolazine is a piperazine derivative with a molecular structure similar to lidocaine (8), a Vaughan-Williams class IB antiarrhythmic drug. Similar to many other antiarrhythmic drugs, ranolazine can inhibit other ion channels. Schram et al. (18) demonstrated that ranolazine inhibits rapidly activating delayed-rectifier K⁺ (I_{Kr}) and Ca²⁺ (I_{Ca}) currents (I_{Kr} > I_{Ca} > I_{Na}) (18). Inhibition of I_{Kr} results in minor prolongation of cardiac action potential duration (APD) (1, 8) and a small increase in the QT interval on ECG (5, 6). That ranolazine prolongs APD, and the QT interval could be proarrhythmic. However, at supraphysiologic doses, ranolazine does not induce EADs or sustained ventricular arrhythmias in experimental models (1, 21). The most likely explanation for ranolazine’s lack of significant proarrhythmia is that the effect of I_{Kr} block is mitigated by inhibition of late I_{Na}^L (1, 8, 21, 28). At clinically relevant concentrations, ranolazine is selective for block of late I_{Na}^L in a 38:1 ratio over peak I_{Na}^L (2). Using a LQT-3 transgenic mouse model, Fredj et al. (8) demonstrated that ranolazine interacts with the SCN5A channel at IVS6 in a use-dependent manner, as do lidocaine, flecainide, and mexilitine, and it is 10-fold greater at blocking the mutant channel activity over wild-type I_{Na}^L. Similar to lidocaine, ranolazine blocks Na⁺ channels in the inactivated state (27). There is also an apparent increased sensitivity of atrial myocytes over ventricular myocytes. Using a canine model, Burashnikov et al. (4) demonstrated that ranolazine exhibits use-dependent block of Na⁺ channels and prolongation of APD_{90} in atrial myocytes but not in ventricular myocytes.

The antiarrhythmic potential for selective blockade of late I_{Na}^L has important clinical implications. The ability of Na⁺ channels to open “late” during the cardiac action potential plateau has been recognized for many years, and it is the increase in late I_{Na}^L that underlies the clinical pathology of LQT-3. An increase in late I_{Na}^L has been postulated to be involved in arrhythmia generation in myocardial ischemia, as shown by ischemia-reperfusion models (12) and heart failure (26, 27). Additionally, the recent report of atrial selectivity of ranolazine may suggest its utility in atrial arrhythmias (4).

Despite its preclinical promise, there is currently limited published clinical trial data to suggest an antiarrhythmic effect for ranolazine. As shown in the Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndrome Thrombolysis in Myocardial Infarction 36 (MERLIN-TIMI 36) trial, which addressed patients with acute coronary syndrome, episodes of nonsustained supraventricular tachycardia and brief runs of ventricular tachycardia were reduced in patients within the first 7 days of treatment with ranolazine compared with placebo (20). Sustained arrhythmias such as new onset atrial fibrillation and ventricular tachycardia were not significantly altered (20), and ranolazine did not affect hard end points of cardiovascular death, myocardial infarction, or recurrent ischemia over 1 yr of treatment (14). What the clinical data do suggest is that ranolazine is safe in patients with a normal QT interval. Further studies are needed to establish the specific antiarrhythmic role(s) of ranolazine.

EADs and DADs. As noted by Song et al. (20a) in their introduction, there is controversy about the role of Ca²⁺ and Ca²⁺ overload as a mechanism for EADs. Although it is not discussed further in this article, their work provides new data.

Address for reprint requests and other correspondence: C. T. January, Room H6/354, CSC, Univ. of Wisconsin, Madison, WI 53792 (e-mail: ctj@medicine.wisc.edu).
Early experimental models suggested that EADs were mainly a surface membrane electrophysiological occurrence that did not depend critically on cell Ca$^{2+}$ or Na$^+$/Ca$^{2+}$ exchange (13). Subsequent studies identified L-type Ca$^{2+}$ channels (11), and possibly Na$^+$ channels (3), as the key charge carrier for EAD depolarization. Action potential lengthening typically precedes EAD generation, and this is thought to result from a decrease in repolarization reserve due to an increase in depolarizing current, a decrease in repolarizing current, or a combination of both. The cellular processes that underlie control of the action potential plateau voltage and repolarization reserve are complex (multiple ion channel currents, Na$^+$/Ca$^{2+}$ exchange, N$^+$/K$^+$ exchange, etc.) and may be altered in disease.

DADs, in contrast to EADs, are thought to occur in the setting of SR Ca$^{2+}$ overload with the spontaneous re-release of Ca$^{2+}$-activating Ca$^{2+}$-dependent depolarizing current(s). DADs and $I_{\text{IT}}$ can be synchronized to the preceding action potential, but SR Ca$^{2+}$ release can also occur spontaneously as sparks and waves.

Thus the central mechanisms for EADs and for DADs were postulated to be different, or are they? More recent experiments using simultaneous optical measurements of membrane voltage and cell Ca$^{2+}$ in myocardium have shown that both change and that this can occur “in phase” or “out of phase.” Observations that EADs and DADs can be generated in the same model system, that the rise in cellular Ca$^{2+}$ can precede EAD depolarization or that inhibition of Na$^+$/Ca$^{2+}$ exchange can block EADs, have been used to argue that EADs and DADs share a common mechanism based on Ca$^{2+}$ overload (7, 17). In the present work by Song et al. (20a), they used isolated guinea pig atrial myocytes and showed an orderly progression of ATX-II-induced action potential lengthening leading first to EAD generation, then DAD generation, and finally DAD-initiated triggered action potentials with the disappearance of EADs. Drugs that reduce Na$^+$ channel late openings (ranolazine and TTX) shortened action potentials and abolished EADs and DADs. In contrast, drugs that did not shorten the action potentials (KB-R7943, ryanodine, EGTA, and BAPTA), but interfered with Ca$^{2+}$ overload-dependent mechanisms, suppressed DAD generation. The data show selective suppression of DADs without blocking EADs, and the findings support the concept that the mechanisms underlying these two types of afterdepolarizations are distinct.

How can these apparent differences between cellular and intact heart models be reconciled? The original models for EADs proposed an overlapping, two-step mechanism. The initial, or conditioning phase, involved establishing conditions that prolong APD (e.g., decrease repolarization reserve), and this can be achieved many ways by modulating various ion channel and/or electrogenic exchange currents. A rise in cell Ca$^{2+}$ would be predicted under most conditions to decrease repolarization reserve by facilitating the inward movement of Na$^+$ ions (and therefore inward current) via electrogenic Na$^+$/Ca$^{2+}$ exchange, and a marked rise in cell Ca$^{2+}$ (such as in ischemia-reperfusion) would be expected to exert an even greater effect. The prolongation of APD would then provide more time for the slow recovery of Ca$^{2+}$, and potentially Na$^+$, channels from inactivation at action potential plateau voltages where the reopening of these channels add inward current for the depolarization phase of EADs. Computational models support the central role of Ca$^{2+}$ channels as the key charge carrier for EADs (29) and for a potential role of cell Ca$^{2+}$ to contribute some charge via Na$^+$/Ca$^{2+}$ exchange current to their initiation (15, 16). Optical imaging studies are limited in that they do not measure transmembrane current. Another confounding factor when attempting to study and compare different models is that the plateau phase of the cardiac action potential, unlike the upstroke, is regulated by multiple small ionic and electrogenic currents, control of Ca$^{2+}$ is complex and dynamic, and these will likely vary between different experimental conditions and disease models (24). Thus, are EADs and DADs generated from a single common mechanism? The answer is, No. But is there overlap of some cellular mechanisms between EADs and DADs? The answer is, Probably yes.

REFERENCES


