Is ranolazine an antiarrhythmic drug?

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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\textsubscript{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, 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\textsubscript{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\textsubscript{TIT}). I\textsubscript{TIT} is a Ca\textsuperscript{2+}-dependent transient inward current thought to be driven by electrogenic Na⁺/Ca\textsuperscript{2+} exchange, Ca\textsuperscript{2+}-activated nonselective cation channels, and possibly Ca\textsuperscript{2+}-activated chloride channels, and it is the depolarizing current associated with DADs (9). The authors propose that increased late I\textsubscript{Na-L} results in intracellular Na⁺ loading, which via Na⁺/Ca\textsuperscript{2+} exchange increases intracellular Ca\textsuperscript{2+} to lead to Ca\textsuperscript{2+}-overload-induced cyclical Ca\textsuperscript{2+} release from the sarcoplasmic reticulum (SR). They then performed additional experiments with their ATX-II action potential model to show that suppression of Na⁺/Ca\textsuperscript{2+} exchange (by KB-R7943) or SR Ca\textsuperscript{2+} release (by ryanodine), or buffering directly cell Ca\textsuperscript{2+} (with EGTA or BAPTA)-suppressed DAD but not EAD generation. There was no attempt to quantify intracellular Na⁺ or Ca\textsuperscript{2+} in these experiments. Overall, the findings show suppression of DADs, DAD-triggered activity, and EADs in a putative Na⁺- and Ca\textsuperscript{2+}-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\textsubscript{K,R}) and slowly activating delayed-rectifier K⁺ (I\textsubscript{Ks}), and Ca\textsuperscript{2+} (I\textsubscript{Ca}) currents (I\textsubscript{Kr} > I\textsubscript{Ca} > I\textsubscript{Ks}) (18). Inhibition of I\textsubscript{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 supraphysiological 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\textsubscript{Kr} block is mitigated by inhibition of late I\textsubscript{Na-L} (1, 8, 21, 28). At clinically relevant concentrations, ranolazine is selective for block of late I\textsubscript{Na-L} in a 38:1 ratio over peak I\textsubscript{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, flecaïnide, and mexiletine, and it is 10-fold greater at blocking the mutant channel activity over wild-type I\textsubscript{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\textsubscript{90} in atrial myocytes but not in ventricular myocytes.

The antiarrhythmic potential for selective blockade of late I\textsubscript{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\textsubscript{Na-L} that underlies the clinical pathology of LQT-3. An increase in late I\textsubscript{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 Ca\textsuperscript{2+} and Ca\textsuperscript{2+} overload as a mechanism for EADs. Although it is not discussed further in this article, their work provides new data.
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, or a combination of both. The cellular processes that increase in depolarizing current, a decrease in repolarizing current, might 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