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EDITORIAL

Arrhythmogenesis and Prolonged Repolarization From Synthetic Opioids: Finally Sorted?

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The synthetic opioid methadone has long been recognized to cause not only QT prolongation on ECG but also a predilection for torsade de pointes.[1,2] Despite the limited distribution of the drug in comparison to other opioids, methadone use has been inordinately implicated in sudden death from ventricular arrhythmia.[3] However, the full mechanistic scope of why this drug is arrhythmogenic has been unresolved.

See Article by Klein et al.

It is well known that the majority of drug-induced long QT and related proarrhythmia is due to inhibition of HERG, which has a promiscuously vulnerable molecular structure, allowing for drugs to directly block the channel or interfere with normal membrane trafficking.[4–6] At first glance, methadone appears to fall in line with respect to HERG inhibition. Katchman et al. demonstrate HERG blockade with methadone that was significantly more potent than other synthetic opioids (eg, fentanyl or morphine).[7] However, on further inspection, the half maximal inhibitory concentration (IC_{50}) was reported at 10-fold higher dose than therapeutic free serum concentrations.[8] Other puzzlingly features have been documented including a lack of consistent correlation between dose and QT interval.[9] Moreover, torsade de pointes in methadone users has been shown to correlate low serum K+ levels and U waves.[10] Interestingly, U waves are an ECG feature that correlate with a higher risk of torsade de pointes, particularly when present postextrasystole.[11] These key features are noted to be implicated with loss of I_{K1}, either genetic (Andersen-Tawil Syndrome) or pharmacologic,[12–14] rather than solely with HERG inhibition.

Predicated on these observations, Klein et al., in this issue of the *Journal of the American Heart Association (JAHA)*,[15] have studied the effect of methadone, as well as the over-the-counter synthetic opioid, loperamide, on I_{K1}. First, using heterologous expression of monomers of the dominant molecular components of I_{K1} for human ventricle, Kir2.1 and Kir2.2, the authors show that methadone exerts a dose response block of both isoforms with an IC_{50} of 2.9 μmol/L for Kir2.1 and 1.2 μmol/L for Kir2.2. Loperamide had a similar effect on Kir2.2 with an IC_{50} of 1.2 μmol/L. Next, using isolated swine ventricular myocytes, the outward (physiologic) component of I_{K1} was effectively blocked by methadone with an IC_{50} of 1.5 μmol/L. The intriguing finding here is the IC_{50} for I_{K1} is lower than previously measured for I_{Kr}[7] and more closely matches reported therapeutic serum levels.

The authors also show action potential (AP) recordings from swine cardiomyocytes exposed to various concentrations of methadone.[15] AP duration at 90% repolarization increased with an associated increase

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in terminal repolarization of the AP, as would be expected with I_{Kr} and I_{K1} blockade. Curiously, at the highest dose (10 μmol/L) where there is potent I_{Kr} and I_{K1} blockade there was AP shortening and slower dV/dT. Unfortunately, further AP characterization (ie, different paced cycle lengths, effect of pause or rapid pacing, etc) and morphologic analysis are not demonstrated. It is loosely hypothesized that AP shortening is due to I_{Na} and I_{Ca} block (as shown by Kuryshev et al.[16]), which fits with their loss of AP plateau. In addition to the AP prolongation, they also indicate the presence of delayed after depolarizations (DADs) at the highest methadone doses (recordings are provided in the Supplemental data) but fail to mention early after depolarizations (EADs) at any methadone concentration as would be expected in drug-induced long QT.

Or would it? How would loss of I_{K1} manifest arrhythmia? And what type (if any) of triggered activity would be expected with loss of I_{K1}? This question is one that my laboratory and others have undertaken; see Reilly and Eckhardt for review.[17] Because of the lack of a specific I_{K1} blocker, to isolate the effect of I_{K1} loss, we have generated several *KCNJ2* (encodes Kir2.1) KI murine models. These mice are modeled from specific patients with Andersen-Tawil Syndrome who all have typical ECG features with U waves, polymorphic ventricular tachycardia (PMVT), and bidirectional VT (some with arrhythmia only under adrenergic stress).[13,18] In a *KCNJ2* KI mouse designed from a patient with adrenergic arrhythmic trigger, we have demonstrated adrenergic dependent loss of I_{K1}.[19] We anticipated finding DADs, the mechanism thought to trigger bidirectional VT,[20] yet these membrane oscillations were relatively slow, infrequent, and rarely reached threshold to trigger a subsequent AP. Moreover, AP analysis and pacing maneuvers with and without adrenergic stimulation also did not induce phase 2 EADs. Instead, we found that the loss of terminal (phase 3) repolarization of the AP resulted in spontaneous phase 3 EADs, present in only the mice heterozygous for the KCNJ2 mutation, not the wild type littermate controls.[19] The phase 3 EADs have a shorter coupling interval to the preceding AP stimulus and more negative takeoff potential (–40 to –55 mV) than phase 2 EADs. In line with this cellular finding, we also found easily inducible PMVT and ventricular fibrillation using ex vivo optical mapping with a single premature ventricular contraction initiation, not a short-long-short pattern anticipated for torsade de pointes in long-QT syndrome.[21,22]

Using computational modeling, we have also shown that loss of I_{K1} can vary by cell type. Modeling loss of I_{K1} combined with gain of late I_{Na} in a purkinje cell model resulted in DADs and sustained arrhythmia.[23] In contrast, the same conditions in a ventricular myocyte model resulted in EAD induction without sustained arrhythmia. Thus, tissue heterogeneity may be part of the missing link to arrhythmia generation with I_{K1} loss.

In correlation with methadone effects on multiple ion channels, important work in using a rabbit model has demonstrated that block of I_{Kr} (with E4031) and I_{K1} (low K+) together increase AP duration and stimulated both phase 2 and phase 3 EADs.[24] In that work, Maruyama et al. elegantly describe the interaction of phase 3 EADs with phase 2 EADs to perpetuate PMVT and ventricular fibrillation, and without phase 3 EADs, triggered activity occurred but arrhythmia did not sustain. Notably, for phase 3 EADs, changes in membrane voltage preceded changes in $[Ca^{2+}]_i$, implicating sodium not calcium as the initial depolarizing current, consistent with other models.[25] Maruyama et al., using the Rudy-Luo computational model, found that loss of I_{K1} was a necessary component to perpetuate PMVT and torsade de pointes.

Putting all of this together, there are several unresolved issues with Klein et al.'s work. Currently lacking are (1) a mechanism(s) of arrhythmogenesis and (2) triggered activity that would reach threshold for a subsequent AP. Their supplemental data show higher concentrations of methadone associate with small membrane oscillations between slow pacing events (0.3 Hz), which may be technically DADs; however, none trigger a subsequent AP nor sustained firing. DADs require SR Ca^{2+} loading to initiate[26] and show typical frequency dependence[27] such that the experimental conditions here are unlikely to produce DADs of sufficient amplitude to initiation arrhythmia. Given the scope of what has already been characterized with loss of I_{Kr} and I_{K1}, one would have expected an investigation for the conditions for EAD induction, both phase 2 and phase 3. Further characterization of the AP, with different pacing frequencies and changing [K+] in external solutions would better elucidate the full effects of methadone and recapitulate conditions associated with its clinical features of arrhythmogenicity. The reasons for the AP shortening also need some flushing out, particularly because the loss of dV/dT may be related to progressive block of I_{K1}, resting membrane potential depolarization and unavailability of sodium channels, as we and others have shown in human ventricular myocytes.[28,29] Such findings could explain the conduction defects in addition to prolonged QT interval noted in loperamide overdoses.[30]

Regardless of the missing pieces, this article highlights the need to look beyond HERG when considering the cardiac safety of new drugs. It long been the purview that HERG inhibition is the barrier to drug safety and, although demonstrating normal HERG current and trafficking is essential, other ionic currents should be considered.[29] Human induced pluripotent stem cells represent a model to resolve this issue, but particular attention needs to be focused on induced pluripotent stem cell cardiomyocytes with normal I_{K1} density.[29,31]

The story with methadone and cardiac toxicity reaches a new (if unresolved) chapter with this insightful work. As the vulnerabilities of loss of I_{K1} are better understood,

mitigation measures for methadone and other arrhythmogenic drugs influence may be finally clarified.

ARTICLE INFORMATION

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