Identifying a Lead Compound for Mitigation of Drug-Induced QTc-Interval Prolongation

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Introduction

Over 175 approved therapeutic drugs list adverse effects which include QT prolongation. Of these, 24% are oncology drugs. Arrhythmic risk is enhanced by the fact that 14-15% of cancer patients present prolonged QT intervals at screening, putting them at risk of developing Torsades de Pointes (TDP) if exposed to QT-prolonging drugs. Triggers for TDP are generally ventricular arrhythmias, which degenerate if there is a substrate for the sustainment of the Torsades. While most Torsades are encoded by the human ether-a-go-go-related (hERG) gene. A substrate feed the Torsades after they are triggered. Over 175 approved therapeutic drugs list adverse effects which sustainment of the current density. Pre-exposure (Baseline) current density was compared to post-exposure levels. * indicate t-tests p ≤ 0.05.

In vitro candidate selection

Patch-clamp current recording.

Manual, whole-cell patch-clamp experiments were conducted at physiological temperature on human embryonic kidney (HEK) cells, line 293 (HEK293), stably transfected with the hERG gene (HEX-HERG). Isolated cells were plated into 2-mL experimental chambers, mounted on the platform of an inverted microscope. The cells were superfused with drug-liposome-containing solutions. A 2.10 MΩ resistance pipette was filled with pipette solution, and brought to contact the external membrane of a single cell.

In vivo candidate selection

Male Hartley guinea pigs (350 - 400; Charles River) were used in these studies. The animals were anesthetized with a mixture of 1.0 to 1.5% isoflurane USP in 95% O₂ and 5% CO₂. The jugular vein was cannulated for i.v infusion of 20 mg/kg moxifloxacin (MF). ECG leads were placed on the animals in a 3-lead configuration. EUB120, 14:0 LysoPG, 16:0 LysoPG, 14:0 EPG and DMPG (Avanti Polar Lipids, Inc.) were administrated as an oral gavage 2 hours prior to the infusion of MF. Three animals were exposed to each PL/MF combination at PLs/MF ratios of 3:1, 1:1 or 0:3:1/n=3). * indicate p ≤ 0.05 from paired t-tests.

Potential mechanisms of action

Flat concentration-response curves for some drugs suggest receptor-lipid interactions. The receptor is likely the hERG channel, with EUB120 binding a site within the pore of the channel, or a site within the cytoplasmic membrane.

Conclusion

Formulation of 14:0 LPG in a eutectic mixture with a myristoyl monoglyceride and myristic acid (EUB120) given orally to guinea pigs prior to i.v infusion of nilotinib, crizotinib and moxifloxacin resulted in significantly reduced QTc prolongation. Four ratios of PLs/MF were tested for mitigation of conduction delays: 3:1, 1:1, 0:3:1, and 0:1:1. Down to 0:3:1 ratio, all the compounds tested mitigated the drug-induced prolongation of QTc intervals. While EPGs induced the most protection, it caused bradycardia and was de-prioritized.

Special thanks