EVALUATION OF CARDIAC LIABILITY OF DRUGS BY TWO IN VITRO FUNCTIONAL ASSAYS

Shimin Wang, Teddy Lin, Karen Bernards, Yulia Ovechkina, Christine O’Day and Dan Small
MDS Pharma Services- Bothell, WA, USA

ABSTRACT
Drug-induced cardiac effects including delayed cardiac repolarization may act as a safety fail point for molecular targets such as ion channel proteins. To date, no single assay can detect all drug-induced cardiac repolarization, two in vitro functional assays are widely employed: (1) the effects of inhibitors on hERG K+ channel current activity and (2) the effects of inhibitors on Purkinje fiber action potentials. Thus, this study used two in vitro functional assays to examine whether Cisapride, Terfenadine and Ketoconazole induced arrhythmias such as Torsades de Pointes or even sudden death.

METHODS
hERG (human ether-a-go-go-related gene) encodes human rapidly activating delayed potassium current, which is essential for the action potential duration (APD) of cardiac myocytes. Drug-induced cardiac toxicity may be due to direct inhibition of hERG channel activity, and can lead to death of cardiac myocytes due to altered membrane potentials.

Three hits from either ventricles in dissection Tyrode solution containing (in mM): NaCl 118; KCl 4; CaCl2 1.8; MgCl2 1.0; NaH2PO4 1.8; NaHCO3 25; glucose 11 (pH 7.4). Eight known hERG K+ channel blockers were tested on HEK-293 cells expressing hERG K+ channel using PatchXpress 7000A. Experiments were performed at ambient temperature. The effects of the eight known hERG K+ channel blockers on hERG K+ channel using PatchXpress 7000A. (2) the effects of inhibitors on Purkinje fiber action potentials. The Purkinje fiber action potentials were recorded at 0.25 and 0.50 s using a multi-channel clamp amplifier. A comparison of our current clamp results with those reported in literature.

CONCLUSION
Eight known hERG K+ channel blockers were tested on HEK-293 cells expressing hERG K+ channel using PatchXpress 7000A. (2) the effects of inhibitors on Purkinje fiber action potentials. The Purkinje fiber action potentials were recorded at 0.25 and 0.50 s using a multi-channel clamp amplifier. A comparison of our current clamp results with those reported in literature.

REFERENCES