Safety Pharmacological Approach for Proarrhythmic Risk Prediction Using IQ-CSRC Drugs (II) - Langendorff Study -

OKoji NAKANO, Fuminori MATSUBARA, Masaru TSUBOI, Kazuhide OKADA, Noriko HASHIGUCHI, Souji MIYAZAKI, Mao YAMAGUCHI, Satomi TOMIZAWA, Rie URA, Taku IZUMI, Hironori OHSHIRO, Hiroshi MATSUKAWA, Akihiro KANNO
Drug Safety Testing Center Co., Ltd., Higashimatsuyama-shi, Saitama, Japan

Introduction
In safety pharmacology studies, it is important to predict the likelihood of proarrhythmic risk. Although in-silico models are now available to predict risk of novel drug candidates, there seems to be room for further improvement. As the Langendorff assay can evaluate direct effect of compounds on the heart, it is well known to be useful in arrhythmogenic-risk prediction. In this research on the Langendorff assay, we tested 6 drugs, which had been evaluated in the clinical QT-prolongation assessment by IQ-CSRC. Additionally we performed detailed analysis of the obtained electrocardiogram.

Methods
Langendorff assay, Animals: guinea-pig
Data Collection:
   Electrocardiogram (HR, RR, PR, QRS, QT, QTc, J-Tpeak, Tpeak-end)
Fridericia’s formula: QTc=QT/RR\(^{1.09}\)
Left-ventricular Pressure (LVPSP, LVEDP, LV dP/dt max)
Drugs:
   DMSO (vehicle), Flecainide, Verapamil, E-4031
Ondansetron, Quinine, Dolasetron, Moxifloxacin, Dofetilide, Levocetirizine
(6 drugs which were used in the IQ-CSRC study)

Results
   DMSO: Vehicle
   Verapamil: Calcium channel blocker
   E-4031: Potassium channel blocker
   Quinine: Multichannel blocking
   Dolasetron: Multichannel blocking
   Dofetilide: \(\mathcal{I}_c\) inhibition

Conclusion
The results indicate that more-sophisticated risk prediction is possible by assessing multiple parameters with the Langendorff assay.