전기생리학 모델을 사용한 부정맥 약물 독성 수준의 전산연구

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Computational Study of Arrhythmic Drugs Toxic Level with Electrophysiology Model

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Abstract : In the past few years, researchers have been pursuing a novel assessment of the drug-induced arrhythmia on the myocytes by involving in-silico methods called CiPA. CiPA stands for Comprehensive in-vitro Proarrhythmia Assessment, which composed by four elements; in-vitro assessment of the drug effects to the cardiomyocytes, in-vivo replication of the EP to analyze the current density, confirm validation of the in-vitro and in-vivo results by using stem cell, and clinical evaluation unanticipated EP effects. In this preliminary study, we focused on the in-silico assessment of the current density under 16 drugs influence. We simulated the drug effects by using human ventricular EP model of O'Hara Rudy model with the partial blocking on the ionic currents. In silico model showed a promising results as an assessment tool of preclinical drug safety test.

1. 서 론

Currently, the biomarkers for a newly developed drug are the prolongation to the hERG channel and the prolongation to the QT interval. Although these constrains are successfully filtered drugs which induced torsade the point (TdP) to the market, however, some of potentially healing drugs that prolonged hERG and QT interval but not induced TdP is also filtered such as ranolazine and verapamil. Hence, the CiPA framework was proposed as a novel protocol to assess the TdP risks from a newly developed drug.

CiPA program was proposed at the Think Tank meeting on July 23, 2013. The meeting was attended by many researchers, pharmaceutical industry, academics, and organizations. it was held in the U.S. Food and Drugs Administration (FDA) headquarters, Maryland. CiPA is a framework which consist of 4 protocols; in-vitro assessment, in silico reconstruction of the EP, in-vitro effects in human stem-cell derived ventricular myocytes, and clinical evaluation of unanticipated EP. This study will be focused on the in silico reconstruction of the EP of the myocytes.

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2. 본 론

The ventricular model used in this study is the model of O'hara Rudy model (2011). In order to incorporate the drug effect, we follow the methods of Mirams et al. which modified the maximum conductance block involving the value of IC50 (the concentration amount of the drug needed for the current to reach half of the activation in nmol) and the concentration of the drugs (denoted by D). The equation is shown as follows:

$$g_i = g_{control,j}\left[1+\left(\frac{[D]}{[IC_{50}]_i}\right)^h\right]^{-1} \quad (1)$$

Where h is hill coefficient, and j is the maximum conductance of j current.

In this study, we followed the data of the conductance block due to the drugs from Crumb et al. study [1]. We measure the risk of the drugs by using qNet following the Dutta et al. from the U.S. FDA [2]. We also obtained data from the Korean Institute of Toxicology.

3. 결 론

Fig. 1 shows the qNet of 16 drugs simulated with the O'Hara Rudy human ventricular model with adjustment in the maksimum conductance. As we can see, the red lines are the drugs with high risk of torsade de point occurrence. The blue and green colors are the intermediate and low risks of TdP occurrence, respectively.

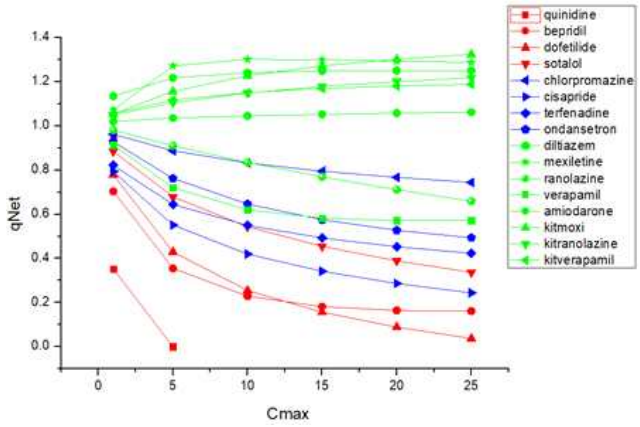

Fig. 1 Reduction of efficiency with the tip clearance and attack angle (Cal. by WFM)

1) In conclusion, In silico model showed a promising results as an assessment tool of preclinical drug safety test.

후 기

This is under progress study. in a full study, we observe the drug effecs under tachyarrhythmia conditions.

참고 문헌

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