Repolarisation Rate: An Integrative Biomarker of cCardiac Action Potential Repolarisation

Ben G Small1,*, David Hollinshead1, Masoud Jamei1, Sebastian Polak1,2

1 Simcyp (a Certara Company); 2 Unit of Pharmacoepidemiology and Pharmacoconomics, Faculty of Pharmacy, Jagiellonian University Medical College, Poland.

Objectives: The pro-arrythmic potential of NCE’s continues to be an issue in drug development [1]. The aim was a preliminary evaluation of the utility of a novel biomarker (ReRa) summarising and discriminating the slope (ΔmV / Δms) between indices of phase II (APD50) and phase III (APD90) cardiac action potential repolarisation.

Methods: Simulation of an epoch (10,000 ms, sampled every 1 ms) of action potentials in both placebo and drug exposed conditions from a single female subject (34 years) was undertaken using the O’Hara-Rudy model [2] in the Cardiac Safety Simulator (CSS v2.0, Simcyp). Input parameters included in vitro measurements of the IC50 and nH (µM) of 6 compounds (Figure) at hERG, Nav1.5, Cav1.2, IKS and IKs and the effective therapeutic plasma concentration (EPTC; µM) of these same compounds [3]. Extraction of the membrane potentials (mV) at which 50 (Vm,50) and 90 (Vm,90) % repolarisation occurred and the corresponding APDx values allowed calculation of the slope between APD50 and APD90 and hence repolarisation rate (ReRa).

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\text{Repolarisation Rate (m / ms)} = \frac{V_{m,90} - V_{m,50}}{\Delta(APD_{90} - APD_{50})}
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Results: ReRa separated bepridil (range = -0.92 to -0.87) from dl-sotalol (-1.04 to -0.98), amiodarone (-1.06 to -1.01), astemizole (-1.07 to -1.02) and dofetilide (-1.07 to -1.02) (Figure). Additional ion channel affinities of bepridil beyond those specified for the other compounds shown here maybe an explantory variable.

Figure: ReRa discriminates between compounds that have different and known propensities to block physiological currents underlying conduction and repolarisation of the cardiac action potential.

Conclusions: Future work will focus on extending this to other compound types and expand this method to understand whether this composite measure can capture inter-subject population variability. This biomarker may have utility as an ‘early’ indicator of pro-arrythmic potential.

References: