Repolarisation Rate: an integrative biomarker of cardiac 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. *Ben.Small@Certara.com

Introduction

Background

The pro-arythmic potential of new chemical entities (NCE’s) continues to be an issue in drug development [1].

Objectives

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 (APD<sub>50</sub>) and phase III (APD<sub>90</sub>) cardiac action potential repolarisation (Fig 1).

Methods

Simulation of an episode or 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 performed using the O’Hara-Rudy model [2] in the Cardiac Safety Simulator (CSS v2.0, Simcyp).

Equation 1.

Repolarisation Rate (mV / ms) = \( \frac{Δ(V_{m,90} - V_{m,50})}{Δ(APD_{90} - APD_{50})} \)

Table 1. Pharmacokinetic and pharmacodynamic ion channel parameters (IC<sub>50</sub> and n<sub>H</sub>) obtained from [3]. Note that the potency of dofetilide (highlighted) at hERG was revised in this table from SP’s personal communication with the authors.

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) (Fig 2). Additional ion channel affinities of bepridil beyond those specified for the other compounds shown here may be an explanatory variable (Fig 2).

Conclusion

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-arrrhythmic potential.

References