Repolarisation Rate: an integrative biomarker of cardiac action potential repolarisation

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Introduction

Background

The pro-arrythmic 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_{50}) and phase III (APD_{90}) cardiac action potential repolarisation (Fig 1).

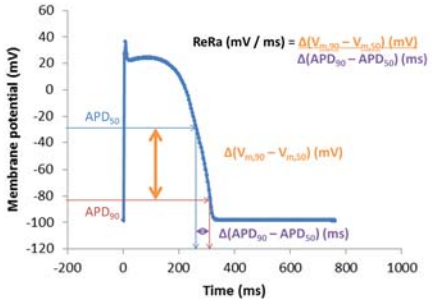

Fig 1. Schematic illustrating the measurement of repolarisation rate (ReRa) from a simulated cardiac action potential (cAP).

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.

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

Input parameters included *in vitro* measurements of the IC_{50} (μM) and n_H of 6 compounds (Table 1) at hERG (I_{Kr}), Nav1.5 (I_{Na}), Cav1.2/b2/a2-d (I_{Ca}), I_{Ks} and I_{to} and the effective therapeutic plasma concentration (ETPC; μM) of these same compounds [3]. Ion channel assemblies were assumed to recapitulate the properties of the physiological current. Extraction of the membrane potentials (mV) at which 50 ($V_{m,50}$) and 90 ($V_{m,90}$) % repolarisation occurred and the corresponding APD_x values allowed calculation of the slope between APD_{50} and APD_{90} and hence repolarisation rate (ReRa; Equation 1).

Table 1. Pharmacokinetic and pharmacodynamic ion channel parameters (IC_{50} and n_H) 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.

Parameter	C_{max}	$ETPC_{unbound}$	I_{Na}		I_{Ca}		I_{Kr}	
	(μg/mL)	(μM)	IC_{50}	h	IC_{50}	h	IC_{50}	h
Drug								
amiodarone	2.5	0.0007747	0.9754	-0.7462	4.832	-0.85	0.7557	-0.8169
astemizol	0.004	0.0002878	1.862	-1.532	0.9878	-2.531	0.02812	-1.745
bepridil	1.27	0.03463	0.6465	-1.155	1.455	-2.317	0.1302	-1.461
cisapride	0.06	0.002579	2.072	-0.894	4.278	-1.378	0.01472	-1.326
dofetilide	0.002	0.0016	2.095	-0.329	2.265	-0.8969	0.038282	-1.983
d,l-sotalol	4	14.68					356.4	1.023
Parameter			I_{Ks}		I_{K1}		I_{to}	
			IC_{50}	h	IC_{50}	h	IC_{50}	h
Drug								
amiodarone								
astemizol								
bepridil			6.0312	-1.779			4.521	-1.853
cisapride								
dofetilide								
d,l-sotalol								

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 maybe an explanatory variable (Fig 2).

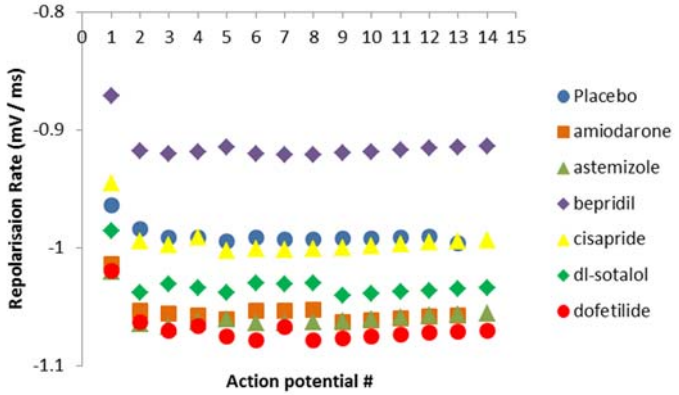

Fig 2. ReRa discriminates between compounds that have different and known propensities to block physiological currents underlying conduction and repolarisation of the cardiac action potential.

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-arrhythmic potential.

References

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3. Okada J-i et al, (2015). Science Advances 1 (4)