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Simulation of early after-depolarisation in non-failing human ventricular myocytes: Can this help cardiac safety pharmacology?

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Abstract:
Background: Identified as being the primary mechanism involved in the induction of torsades de pointes (TdP), early after-depolarisation (EAD) formation is an important parameter in cardiac safety pharmacology. Easily observed experimentally at the cellular or tissue level, EAD can also be simulated by computer algorithms using animal or human models. During the last decade, confidence in these algorithms has greatly increased. We investigated the putative usefulness of EAD simulation for cardiac safety pharmacology.
Methods: EAD simulations were performed in non-failing human ventricular myocytes using the O'Hara-Rudy dynamic model. The role of each cardiac current was investigated by modifying the amplitude of its activity in the model. Prediction of EAD induction by drugs was based on the ratio of their 50% inhibitory concentration values for various cardiac ionic currents to their maximal effective free therapeutic plasma concentration ($EFTPC_{max}$).
Results: In the ventricular endocardial myocytes, EAD was only induced by at least 85% inhibition of the rapid delayed rectifier K^+ current (I_{Kr}). The other currents can either induce or prevent EAD under sub- (80% I_{Kr} inhibition) or up-threshold conditions (87% I_{Kr} inhibition) of EAD. The study of the ability of drugs to induce EAD resulted in a classification which was in agreement with the Tdp risk classification.
Conclusion: Based on EAD computer simulation within the human situation, the present study identified the role of various cardiac currents in the EAD formation and suggested that prediction of EAD formation can be useful for early cardiac safety pharmacology.

Key words:
early after-depolarisation, safety pharmacology, cardiac action potential simulation, ORd model, maximal effective free therapeutic plasma concentration

Abbreviations: AP – action potential, APA – maximal AP amplitude, APD_{xx} – action potential duration at xx percent of the APA, CL – cycle length, EAD(s) – early after-depolarisation(s), $EFTPC_{max}$ – maximal effective free therapeutic plasma concentration, ORd model – O'Hara-Rudy dynamic model, RMP – resting membrane potential, TdP – torsades de pointes, T_{xx} – triangulation at xx percent of APA, V_{max} – maximal rate of AP rise

Introduction

During the process of drug candidate discovery and/or development, reduction of the attrition rate is a major concern that remains to be solved by the pharmaceutical industry. Achieving this goal has strongly influ-

enced the fast emergence of scientific safety pharmacology in order to try to reveal cardiac liability earlier in this research process [3, 33, 38]. Among the various biomarkers that have been proposed for use in cardiac safety pharmacology, inhibition of the rapid delayed rectifying K^+ channel current (I_{Kr}) is crucial [34 for review]. This current controls the repolarisation of cardiomyocytes and a delay in this repolarisation leads to an abnormally long action potential (AP) often associated with an increased risk of cardiac arrhythmias. Nevertheless, various other cardiac ionic currents also influence this AP prolongation so that a multiple ion channel block is recognized as important for improving the early prediction of drugs' clinical torsadogenic risk [23]. The formation of early after-depolarisations (EADs) is also an important parameter in cardiac safety pharmacology as EADs are identified as being the primary mechanism involved in the induction of torsades de pointes (TdP) [2, 11, 15, 16]. EADs, defined as depolarisations occurring before the completion of AP repolarisation, are often associated with abnormally long AP observed with bradycardia or in the presence of a drug inducing prolongation of the action potential duration (APD) [5, 40, 41]. These EADs, generated in the presence of transmural heterogeneity during the ventricular repolarisation, can induce abnormal rhythmic cardiac activity resulting in severe cardiac arrhythmias such as TdP, polymorphic ventricular tachycardia or ventricular fibrillation. Easily observed experimentally at the cardiac cellular or tissue level of various species [4, 7, 12, 14, 16, 39], EAD induction has been demonstrated to be tissue- [17] and species-dependent [28]. On the other hand, EAD can also be simulated by computer algorithms using animal or human models. During the last decade, confidence in these algorithms has greatly increased [24]. Up to now, the recent O'Hara-Rudy dynamic (ORd) model based on isolated non-failing human ventricular myocytes [29] has been the only algorithm able to reproduce EAD within the human situation. Therefore, the present study using the ORd model is focused on EAD in order to determine the conditions and threshold of EAD formation in the human species and the factors inducing or suppressing EAD under sub- or up-threshold conditions of EAD. Finally, the opportunity to predict EAD induction by various drugs is studied and the putative role of EAD simulation in cardiac safety pharmacology is discussed.

Materials and Methods

The ORd model equations used in the present study were fully described in O'Hara et al. [29] and in the research section of their website: http://rudylab.wustl.edu. Constants (extracellular ionic concentrations, cell geometry, channel conductance), initial conditions for state variables and scaling factors (applied to various ionic fluxes or to the conductance of various channels allowing differences among endo-, mid- and epimyocardial cells to be tested) were used as described in the ORd model. Simulations were carried out at equilibrium (after 100 beats) under a cycle length (CL) of 4000 ms in order to facilitate EAD formation. The impact of each current variation was calculated using the main equation of the model:

$$dv/dt = -(1 / Cm) \times (I_{tot} + I_{stim}) \quad (1)$$

where: dv = voltage membrane variation, dt = time variation, Cm = membrane capacitance, I_{tot} = sum of the various ionic currents and I_{stim} = stimulus current.

These various currents were I_{Na} (fast Na^+ current), I_{NaL} (late Na^+ current), I_{to} (transient outward K^+ current), I_{CaL} (Ca^{++} current through the L-type Ca^{++} channel), I_{CaNa} (Na^+ current through the L-type Ca^{++} channel), I_{CaK} (K^+ current through the L-type Ca^{++} channel), I_{Kr} (rapid delayed rectifier K^+ current), I_{Ks} (slow delayed rectifier K^+ current), I_{K1} (inward rectifier K^+ current), I_{NaCai} (myoplasmic component of Na^+/Ca^{++} exchange current), I_{NaCass} (subspace component of Na^+/Ca^{++} exchange current), I_{NaK} (Na^+/K^+ adenosine triphosphatase current), I_{Nab} (Na^+ background current), I_{Kb} (K^+ background current), I_{pCa} (sarcolemmal Ca^{++} pump current) and I_{Cab} (Ca^{++} background current).

The activity of all these various currents resulted in an AP linked to voltage membrane variations induced by a single electrical stimulation. This AP was described by using the following parameters: resting membrane potential (RMP) expressed as millivolts (mV), maximal amplitude of the AP (APA) expressed as mV, maximal rate of AP rise (V_{max}) expressed as volts per second (V/s), duration of the AP measured at 40, 60 or 90% of APA inhibition ($APD_{40,\ 60\ or\ 90}$) expressed as milliseconds (ms) and finally AP triangulation estimations which were the difference between APD_{90} and APD_{40} or APD_{60} ($T_{40\ or\ 60}$) expressed as ms.

The shape of this AP can be modified by scaling either individually or simultaneously the conductance of these channels [6, 23]. Nevertheless, drugs influ-