In silico assessment of antiarrhythmic effects of drug ranolazine on electrical activity in human ventricular myocardium

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Introduction

Ranolazine is an antianginal compound without significant hemodynamic fluctuations (e.g bradycardia or hypotension), approved by the US Food and Drug Administration (FDA). Although several experimental studies have shown a potent antiarrhythmic effect of ranolazine against cardiac (atrial and ventricular) arrhythmias, the potential antiarrhythmic effects of ranolazine need to be investigated in humans. The objective was to determine the antiarrhythmic effects of ranolazine on the human ventricular electrophysiology and to describe the ionic mechanisms of these effects. For this purpose, a combination of ranolazine with class III antiarrhythmic drugs (dofetilide and d,1-sotalol) is used to examine the effects of inhibition of I_{NaL} on top of I_{Kr} block**.**

Methods

The impact of dose/concentration relationship of drugs on ventricular arrhythmias biomarkers (i.e. APD, ΔAPD) was demonstrated. We obtained ΔAPD values (ΔAPD = APD with ionic current inhibition (Table 1,2 and 3) – APD placebo (under control conditions)) from simulation models using experimental values from [1,2]. We used the Cardiac Safety Simulator (CSS V2.0, Simcyp, Sheffield) to evaluate the cardiac electrophysiological effects of ranolazine and its interaction with two class III antiarrhythmic drugs. Simulations were performed in O'Hara-Rudy dynamic (ORd) [3] human ventricular model by using data presented in Table 4, in order to test the potent late sodium (I_{NaL}) blocking actions of ranolazine on suppressing arrhythmias induced by dofetilide and d,1-sotalol at different concentration.

Table 1. IC_{50} and concentration values ranolazine on ion channels *in vitro*

Effects of ranolazine on cardiac transmembrane ion currents [1]						
Ion Channel current			Inhibitory Potency I_{C50} (μM)			
Inward	I_{Na}		294			
	I_{NaL}		5.9			
	I_{CaL}		296			
Outward	I_{Kr}		11.5			
	I_{Ks}		30			
	I_{K1}		no effect			
	I_{to}		no effect			
Drug concentration (μM)	Placebo	2	4	5	10	15*

Table 2. Drug concentrations and inhibitory actions of dofetilide on ion channels in vitro

Inhibitory actions of dofetilide on ion channels [2]								
Fraction conc.	$ETPC_{unbound}$ (μm)	I_{Na}		I_{Ca}		I_{Kr}	
		I_{C50}	h	I_{C50}	h	I_{C50}	h
×1	0.0016	124.45	0.32	184.1	0.89	0.038	1.98
×10	0.016						
×30	0.048						
×50	0.08						
×75	0.12						

Table 3. Drug concentrations and inhibitory actions of d,1-sotalol on ion channels in vitro

Inhibitory actions of d,1-sotalol on ion channels [2]			
Fraction conc.	$ETPC_{unbound}$	I_{Kr}	
		I_{C50}	h
×1	14.68	356.4	1.023
×10	146.8		
×50	734		
×75	1101		
×100	1468		

Table 4. Drug concentrations data to assess drug-drug interactions of ranolazine with two unsafe compounds

Ranolazine effects on dofetilide and d,1-sotalol					
Substrate	Drug concentration (μM)				
ranolazine	15				
dofetilide	0.0016	0.016	0.048	0.08	0.12
d,1-sotalol	14.68	146.8	734	1101	1468

Results and discussion

- Ranolazine has no effect on resting membrane potential and AP amplitude (Figure 1).
- Ranolazine caused a small concentration-dependent lengthening of APD in endo cell (Figures 1 and 2).
- The ΔAPD increasingly grows by increasing dose for d,1-sotalol and dofetilide (Figures 3 and 4).
- The concentration-dependent prolongation of APD that was greater at 90% than at 50% repolarization.
- APD prolongations is shown for d,1-sotalol and dofetilide associated with the Class III action of blocking I_{Kr} which can lead to torsade de points.
- Despite primary prolongation of APD of the in-vitro-modelled electrophysiology on both drugs, ranolazine shortens the APD (Figures 5 and 6), leading to suppression of the dofetilide and d,1-sotalol for the initiation/maintenance of ventricular arrhythmias.

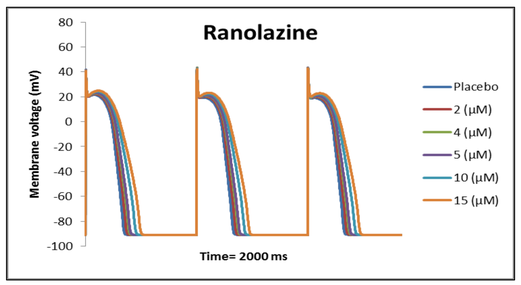


Figure 1. Concentration-dependent effects of ranolazine on cellular APs in the ORd endocardial human cell model.

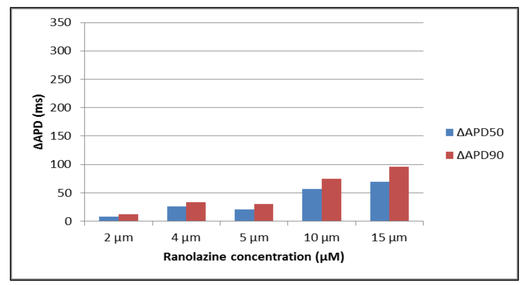


Figure 2. Concentration-dependent effects of ranolazine on ΔAPD mutation

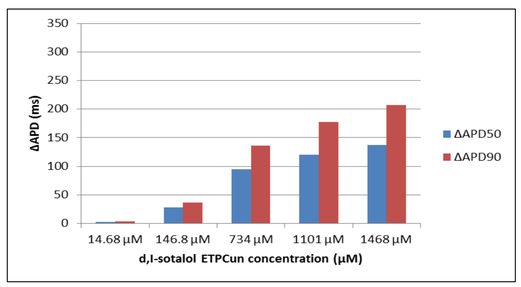


Figure 3. Concentration-dependent effects of d,1-sotalol on ΔAPD mutation in human ventricular myocyte.

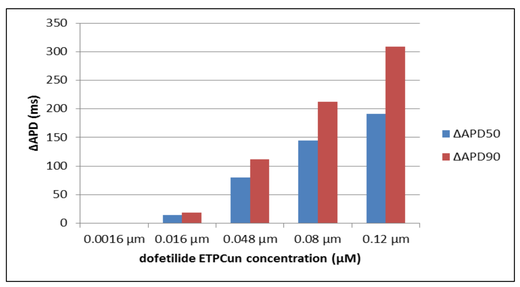


Figure 4. Concentration-dependent effects of dofetilide on ΔAPD mutation in human ventricular myocyte.

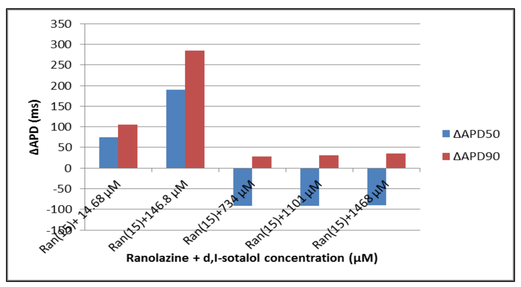


Figure 5. Impact of ranolazine, with combination of different d,1-sotalol plasma concentrations on ΔAPD mutation in human ventricular myocyte.

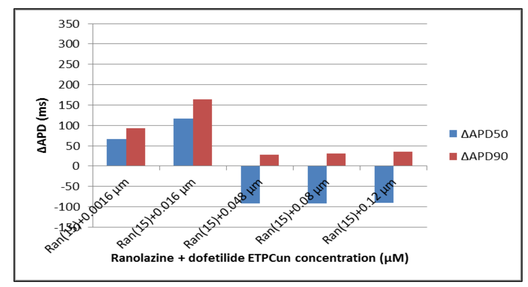


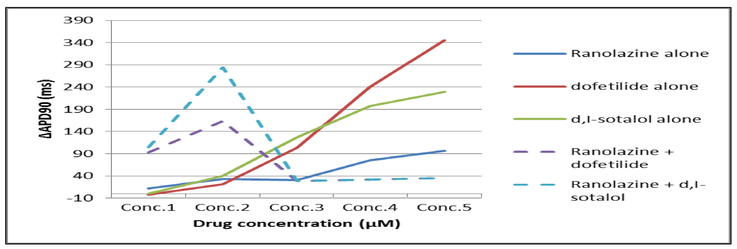
Figure 6. Impact of ranolazine, with combination of different dofetilide plasma concentrations on ΔAPD mutation in human ventricular myocyte.

Conclusions

- The sensitivity of ionic currents to ranolazine was described as Action Potential Duration (APD) variations in response to different therapeutic concentrations.
- Although ranolazine slightly prolonged APD, it reduced the increase in APD induced by the selective I_{Kr} blockers d-sotalol and dofetilide in human cardiac ventricles (Figure 7), which demonstrate the pharmacological effect of ranolazine includes inhibition of I_{NaL}, I_{CaL} and I_{Kr} currents.
- Simulation results are in agreement with in vitro and in vivo studies of arrhythmia and confirmed the antiarrhythmic properties of ranolazine which may be utilized for suppressing ventricular arrhythmias.

Drug-Drug Interactions

Figure 7. Summary of electrophysiological effects of compounds on ventricular moyocytes and their interactions with ranolazine. Conc. represents drug plasma concentrations used individually or in combination with drugs (Table 4).



References

1. Antzelevitch C, Burashnikov A, Sicouri S, Belardinelli L. Electrophysiological Basis for the Antiarrhythmic Actions of Ranolazine. October. 2011;141(4):520–9. 2. Okada J -i., Yoshinaga T, Kurokawa J, Washio T, Furukawa T, Sawada K, et al. Screening system for drug-induced arrhythmogenic risk combining a patch clamp and heart simulator. Sci Adv. 2015;1(4):e1400142–e1400142. 3. O'Hara T, Virág L, Varró A, Rudy Y. Simulation of the undiseased human cardiac ventricular action potential: model formulation and experimental validation. PLoS Comput Biol. 2011 May;7(5):e1002061.