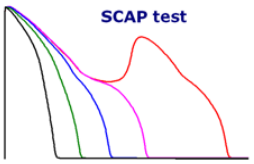
Safe Cardiac Action Potential Test



Drug

Dofetilide

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 26.7 µM (1.0)
I_{to} : ---- µM (---)
I_{Kr} : 0.030 µM (1.2)
I_{NaL} : ---- µM (---)
I_{Na} : 162.1 µM (1.0)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ [1]

0.002 µM

TdP risk

Redfern [2] : class IA or III antiarrhythmics (class 1)
Kramer [3] : torsadogenic (class 1)
CredibleMeds [4] : known risk of TdP (class 1)
CiPA [5] : high risk of TdP (class 1)
WP [6] : 16/0 (TdP+/TdP-)

Results

In silico cardiac action potential study (ORd model) [7]

Simulation conditions:
- Cell geometry, channel conductance, state variables and scaling factors for endo-, mid- and epicardial myocytes as described in ORd model
- External ionic concentrations (mM): $[Na^+]_o$ 140 - $[Ca^{++}]_o$ 1.8 - $[K^+]_o$ 5.4
- Cycle length : 1000 msec
- Beat number: 100

Effect of drugs on AP [8]:
- channel conductance modified by a scaling factor ranked from 1 (no inhibition) to 0 (full inhibition) which is a function of a multiple of $EFTPC_{max}$ and IC_{50s}

$$I_j = g_j O(V - E_{ion})$$

g_j = maximal conductance of channel 'j'
O=open probability of channel 'j'
V= voltage membrane
E_{ion} = reversal potential for species of ions which flows through channel 'j'

$$g_j = g_{j(control,j)}\left[1+\left(\frac{D}{(IC50_j)}\right)^n\right]^{-1}$$

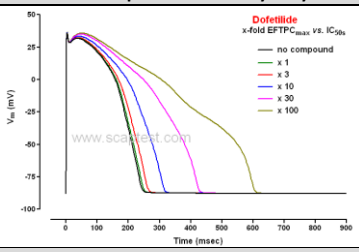
$g_{j(control,j)}$ = drug free maximal conductance of channel 'j'
IC50 = 50% of inhibition of a drug for channel 'j'
D= drug concentration (EFTPC for example)
n= hill slope

TDR and RUD estimation:
- TDR = APD_{90} mid - APD_{90} epi (at CL of 1000 msec)
- RUD = $APD_{30}P_{4000}$-$APD_{30}P_{1000}$

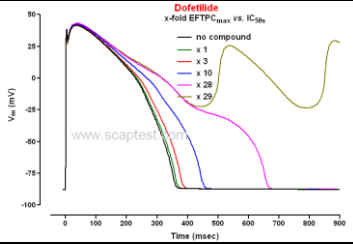
where
$APD_{30}P_x$ = APD_{30} with - APD_{30} without compounds at CL x

IC index calculation [9]:
IC index = (AFKr/((AFNaL+AFCaL)/2))*100
where
AFKr, AFNaL and AFCaL = active fraction (%) of the I_{Kr}, I_{NaL} and I_{CaL}.

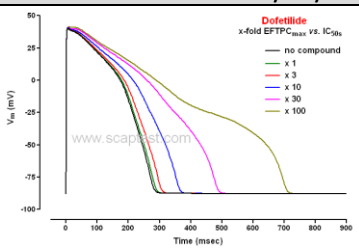
Human epicardial myocytes



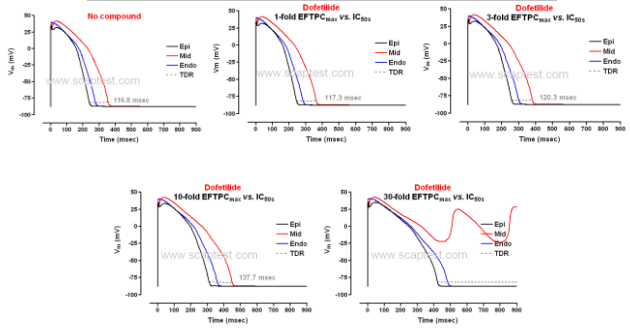
Human midmyocardial myocytes



Human endocardial myocytes

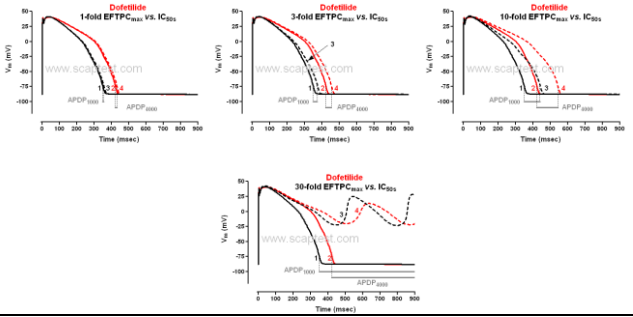


Transmural dispersion of repolarisation

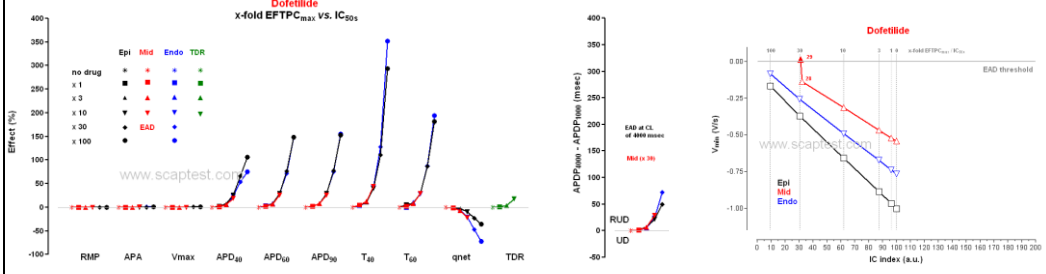


Reverse use dependence on midmyocardial myocytes

1 - CL 1000 msec without compound
2 - CL 4000 msec without compound
3 - CL 1000 msec with compound
4 - CL 4000 msec with compound



Summary



References

1. Kramer J et al. (2013) *Sci.rep.* **3** : 2100
2. Redfern WS et al. (2003) *Cardiovasc. Res.* **58** : 32-45
3. Kramer J et al. (2013) *Sci.rep.* **3** : 2100
4. Woosley RL (2015) www.CredibleMeds.org
5. CiPA (2016) www.ilsiextra.org/hesi/science/cardiac/cipa/Project
6. Wisniowska et al. (2017) *Drug discovery today* **22** : 10-16
7. O'Hara T et al. (2011) *PLoS Comput. Biol.* **7** : e1002061_8
8. Mirams GR et al. (2011) *Cardiovasc. Res.* **91** : 53-61
9. Christophe B et al. (2019) *J Pharmacol Toxicol Methods* **96** : 15-26

Abbreviations

AP : action potential, APA : AP amplitude , $APD_{40, 60 or 90}$: AP duration at 40, 60 or 90 % of APA, APDP : APD prolongation, CL : cycle lenght , EFTPCmax : maximal effective free therapeutic plasma concentration , IC_{50} : 50% inhibition concentration, msec : millisecond, mV : millivolt, qnet: integration sum of I_{CaL}+I_{to}+I_{Kr}+I_{to}+I_{NaL}+I_{K1} , RMP : resting membrane potential , RUD : reverse use dependence, $T_{40, 60}$: APD_{90}-APD_{40} or APD_{60} (~triangulation)
TdP : torsade de pointes , TDR : transmural dispersion of repolarization, V_m : membrane voltage, V_{max} : maximal rate of AP rise , V_{min} : minimal rate of AP decrease at EAD take-off voltage

Comments to be sent to: bchristophe@scaptest.com *see also: Pharm.Rep. (2013) **65**:1281-1293, Br.J.Pharmac.Res. (2015) **7**:88-101 or Toxicol.Appl.Pharmacol. (2022) **438**:115914*