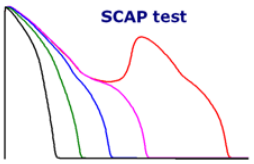
Safe Cardiac Action Potential Test



Drug

Dofetilide

Potassium voltage-gated cardiac channel ($K_v11.1$) blocker used as class III antiarrhythmic to treat cardiac arrhythmia
no longer marketed in Europe (Onakpoya et al (2016) *BMC Med.* **14**: 10)

Raw data

IC_{50s} (slope) [1]

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

$EFTPC_{max}$ [1]

0.002 µM

TdP risk

Redfern [2] : class IA or III antiarrhythmics (class 1)
Kramer [3] : torsadogenic (class 2)
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}

$I_j = g_j O (V - E_{ion})$; $\theta_j = g_{control,j}\left[1 + \left(\frac{D}{IC50_j}\right)^n\right]^{-1}$

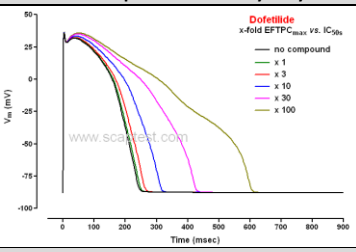
g = maximal conductance of channel 'j'
O = open probability of channel 'j'
V = voltage membrane
E_{ion} = reversal potential for species of ions which flows through channel 'j'
$g_{control,j}$ = drug-free maximal conductance of channel 'j'
IC50 = 50% of inhibition of a drug for channel 'j'
D = drug concentration (EFTPC for example)
n = hill slope

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

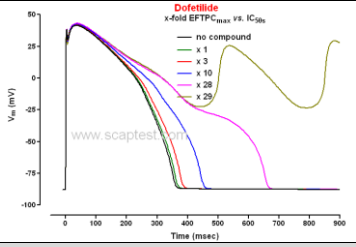
where
$APD_{90}P_x$ = APD_{90} with - APD_{90} without compound at CL x

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}

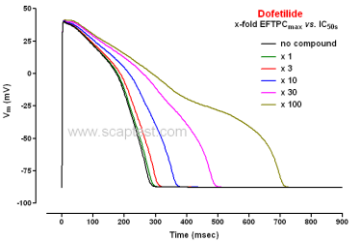
Human epicardial myocytes



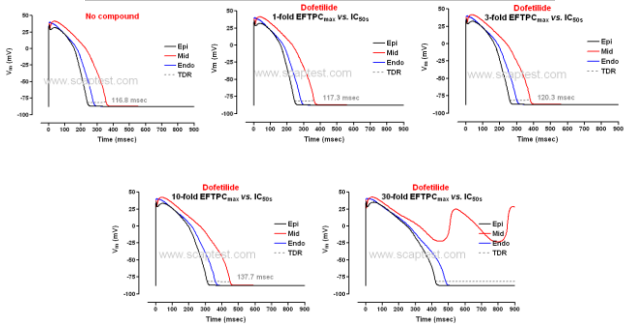
Human midmyocardial myocytes



Human endocardial myocytes

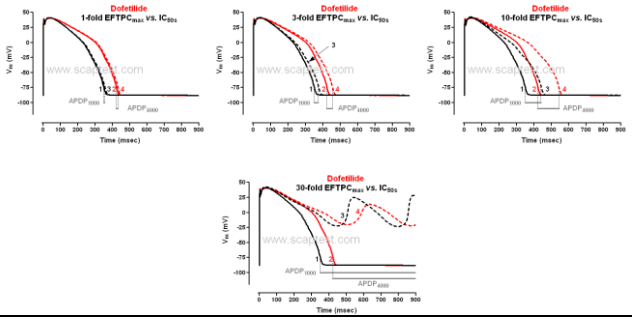


Transmural dispersion of repolarisation

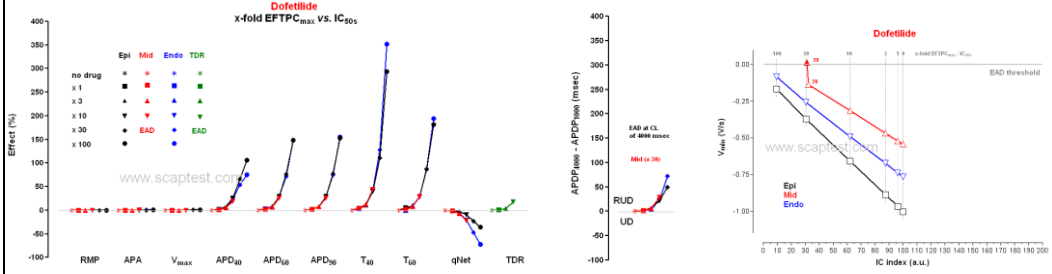


Reverse use dependence on midmyocardial myocytes

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

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4. Woosley RL (2015) www.CredibleMeds.org
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7. O'Hara T et al. (2011) *PLoS Comput. Biol.* **7** : e1002061_8
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9. Christophe B & Crumb WJ Jr (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, **a.u.** : arbitrary unit, **CL** : cycle lenght , **DA** : depolarization abnormalities, **EAD** : early afterdepolarization, **EFTPCmax** : maximal effective free therapeutic plasma concentration, **endo** : endocardial myocyte, **epi** : epicardial myocyte, **IC index** : ion channel inhibition index, **IC_{50}** : 50% inhibition concentration, **mid** : midmyocardial myocyte, **msec** : millisecond, **mV** : millivolt, **qNet** : integration sum of I_{CaL}+I_{to}+I_{Na}+I_{NaL}+I_{Kr}, **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, **V/s** : volt per second

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*