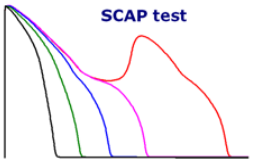

Safe cardiac action potential test (www.scaptest.com) : a database describing the *in silico* cardiac safety profile of drugs and their propensity to induce early afterdepolarization

Part II : description of 50 additional drugs

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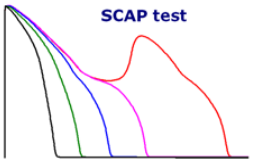
doi: 10.5281/zenodo.13913353

October 2024 – version 1.0 – 50 drugs

Electronic citation:

Christophe B. (2024) Safe cardiac action potential test (www.scaptest.com): a database describing the *in silico* cardiac safety profile of drugs and their propensity to induce early afterdepolarization (part II: description of 50 additional drugs) .doi: 10.5281/zenodo.13913353



Aim of the database

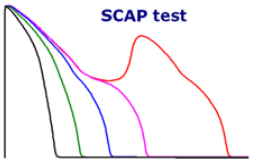
The aim of the present database is to describe the *in silico* cardiac safety profile of drugs and their propensity to induce early afterdepolarization. This is based on the study of the effects of drugs on the non-failing human ventricular myocyte (endo-, mid- and epicardial subtypes) action potential reconstructed by computational simulation (O'Hara-Rudy dynamic algorithm) in order to identify cardiac action potential abnormalities such as high variations and/or occurrence of:

- resting membrane potential (RMP)
- action potential amplitude (APA)
- maximal rate of action potential rise (V_{max})
- action potential duration (APD)
- triangulation (T)
- early afterdepolarization (EAD)
- transmural dispersion of repolarization (TDR)
- reverse use dependence (RUD)
- integrated sum of $I_{CaL} + I_{Kr} + I_{Ks} + I_{NaL} + I_{to} + I_{K1}$ (qNet)
- minimal rate of action potential decrease at EAD take-off voltage (V_{min})

These various parameters are useful in order to assume a more accurate predictability of pro-arrhythmic liabilities of new drug candidate in the cardiac safety pharmacology screening process, which is the aim of the comprehensive *in vitro* pro-arrhythmia assay (CiPA) initiative.

The *in silico* cardiac safety profile of each drug (150 drugs described in this first version) is illustrated by a separate page describing the effects induced by each compound on these various parameters.

The results are summarized regarding the expected pro-arrhythmia profile of the various compounds as described by the CredibleMeds classification evaluating their propensity to induce torsade de pointes.



Algorithm used

- ORd model: O'Hara T, Virág L, Varró A, Rudy Y (2011) Simulation of the undiseased human cardiac ventricular action potential: model formulation and experimental validation. PLoS Comput Biol, 7(5):e1002061.

Simulation conditions

- Cell geometry : as described in ORd model
- Channel conductance: as described in ORd model
- State variables: as described in ORd model
- Scaling factors among endo-, mid- and epi myocardial cells: as described in ORd model
- External ionic concentrations : $[Na^+]_o$, $[Ca^{++}]_o$ and $[K^+]_o$ of 140, 1.8 and 5.4 mM
- Cycle length (CL): 1000 msec
- Beat number: 100

Action potential reconstruction

- Calculation of action potential parameters from endo-, mid- and epicardial myocytes in the absence and the presence of drug.
- Drug tested at 1-, 3-, 10-, 30- and 100-fold $EFTPC_{max}/IC_{50s}$ ratios (maximal effective free therapeutic concentration divided by 50% inhibition concentration induced by a compound on each cardiac ionic current). More precise x-fold determined in case of EAD occurrence.

Effect of drugs on ion channel

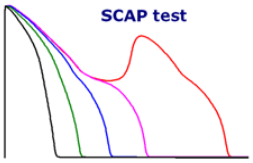
- Conductance of the channel (g_j) modified by a scaling factor ranked from 1 (no inhibition) to 0 (full inhibition) determined from the tested $EFTPC_{max}/IC_{50s}$ ratio.

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

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'

$$g_j = g_{control,j}\left[1 + \left(\frac{D}{[IC50]_j}\right)^n\right]^{-1}$$

g_j = maximal conductance of 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 estimation methodology

- Calculation of action potential duration (APD_{95}) from epi- and midmyocardial myocytes at CL of 1000 msec

- TDR = APD_{95mid} - APD_{95epi}

RUD estimation methodology

- Calculation of action potential duration prolongation ($APD_{90}P$) induced by a compound (*vs.* absence of compound) on the midmyocardial myocytes at CL of 1000 and 4000 msec

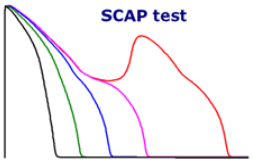
- RUD = $APD_{90}P_{4000}$-$APD_{90}P_{1000}$ where

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

Calculation of the Ion Channel inhibition index

- IC index = $(AF_{Kr}/((AF_{NaL}+AF_{CaL})/2))*100$ where

AF_{Kr}, AF_{NaL} and AF_{CaL} = active fraction (%) of I_{Kr}, I_{NaL} and I_{CaL} currents in the presence of compound calculated from each $EFTPC_{max}/IC_{50s}$ ratio tested.



Classification of compounds regarding their torsade de pointes (TdP) risk

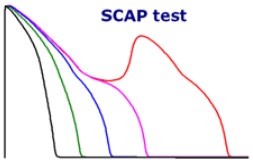
- **Redfern** TdP risk classification : (Cardiovasc Res 2003, 58 : 32-45)
    - Class 1 (class IA or III anti-arrhythmics with large but acceptable TdP risk)
    - Class 2 (compounds withdrawn from the market due to unacceptable TdP risk)
    - Class 3 (compounds with numerous TdP reports)
    - Class 4 (compounds with isolated TdP reports)
    - Class 5 (compounds without any published TDP reports).

- **CredibleMeds** TdP risk classification : (www.crediblemeds.org)
    - Class 1 (compounds with risk of TdP)
    - Class 2 (compounds with possible risk of TdP)
    - Class 3 (compounds with conditional risk of TdP)
    - Class 4 (compounds reviewed but not classified in class 1, 2 or 3)

- **Kramer** TdP risk classification: (Sci Rep 2013, 3 : 2100)
    - Class 1 (torsadogenic compounds)
    - Class 2 (non-torsadogenic compounds)

- **CiPA** TdP risk classification: (www.ilsiextra.org/hesi/science/cardiac/cipa/Project)
    - Class 1 (compounds with high risk)
    - Class 2 (compounds with intermediate risk)
    - Class 3 (compounds with low risk)

- **Wiśniowska and Polak** TdP risk classification: (Drug discovery today 2017, 22 : 10-16)
    - xx /xx (number of studies with TdP+ or TdP- reports)



Drug

Alosetron

Serotonin 5-HT_3 receptor antagonist used to treat diarrhea-predominant irritable bowel syndrome
no longer marketed in USA (Onakpoya et al (2016) *BMC Med.* **14**: 10)

Raw data

IC_{50s} (slope) [1]

I_{CaL} : ---- µM (---)
I_{Kr} : 3.2 µM (1.0)
I_{Na} : ---- µM (---)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$

0.00467 µM

Kock KM et al (2004) Aliment Pharmacol Ther **20**: 223-230

TdP risk

Redfern [2] : not reported
Kramer [3] : not reported
CredibleMeds [4] : not classified with TdP risk (class 4)
CiPA [5] : not reported
WP [6] : not reported

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}

$I_j = g_j O(V - E_{ion})$; $g_j = g_{control,j}\left[1+\left(\frac{D}{[IC50]_j}\right)^{n_j}\right]^{-1}$

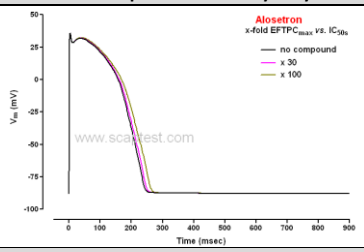
g = maximal conductance of channel 'j'
O=open probability of channel 'j'
V= voltage membrane
E_{ion}= reversal potential for species of ions which flows through channel 'j'
$g_{control,j}$ = drug-free maximal conductance of channel 'j'
IC50 = 50% of inhibition of a drug for channel 'j'
D= drug concentration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

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

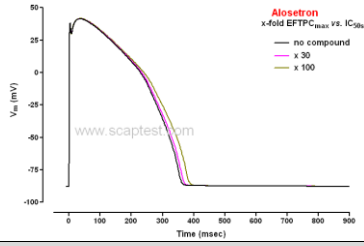
where
$APD_{90}P_x$ = APD_{90} with - APD_{90} without compound at CL x

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}

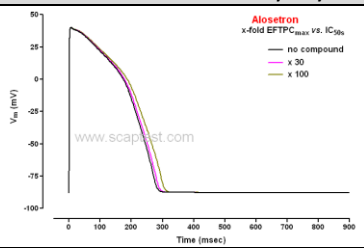
Human epicardial myocytes



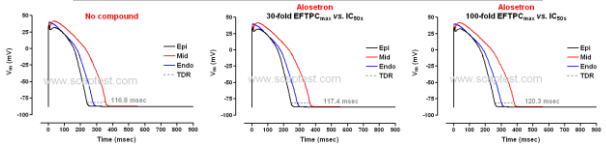
Human midmyocardial myocytes



Human endocardial myocytes

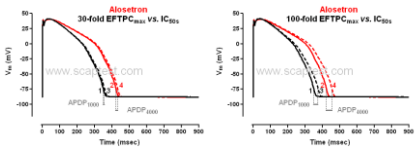


Transmural dispersion of repolarization

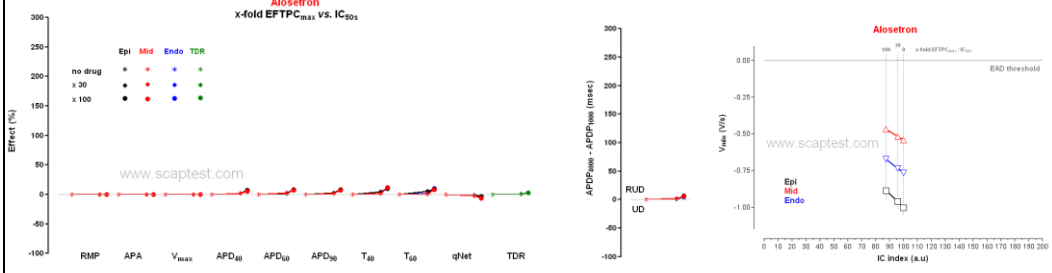


Reverse use dependence on midmyocardial myocytes

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



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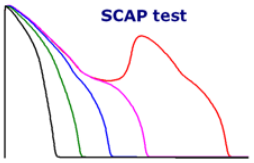
4. Woosley RL (2015) www.CredibleMeds.org
5. CiPA (2016) www.ilsiextra.org/hesi/science/cardiac/cipa/Project
6. Wiśniowska B et al. (2017) *Drug discovery today* **22 :** 10-16
7. O'Hara T et al. (2011) *PLoS Comput. Biol.* **7 :** e1002061_8
8. Mirams GR et al. (2011) *Cardiovasc. Res.* **91 :** 53-61
9. Christophe B & 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_{Kr}+I_{Ks}+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, **V/s** : volt per second



Drug

Aprindine

Potassium voltage-gated cardiac channel ($K_v11.1$) and Na^+/Ca^{++} exchange blocker used as Class Ib antiarrhythmic to treat arrhythmias

Raw data

IC_{50s} (slope) [1]

I_{CaL} : ---- µM (---)
I_{to} : ---- µM (---)
I_{Kr} : 0.23 µM (1.0)
I_{NaL} : ---- µM (---)
I_{Na} : ---- µM (---)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ [1]

0.239 µM

TdP risk

Redfern [2] : numerous TdP reports (class 3)
Kramer [3] : not reported
CredibleMeds [4] : not reported
CiPA [5] : not reported
WP [6] : 2/0 (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'

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

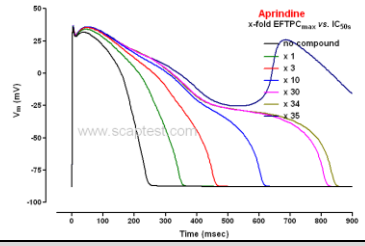
$g_{control,j}$= drug-free maximal conductance of channel 'j'
IC50 = 50% of inhibition of a drug for channel 'j'
D= drug concentration (EFTPC for example)
n = hill slope

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

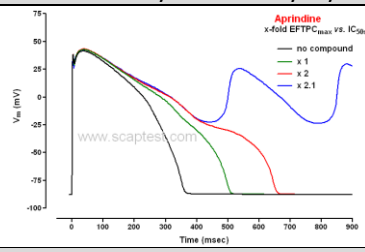
where
$APD_{90}P_x$ = APD_{90} with - APD_{90} without compound at CL x

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

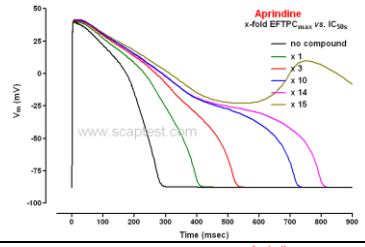
Human epicardial myocytes



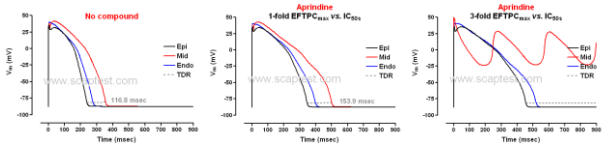
Human midmyocardial myocytes



Human endocardial myocytes

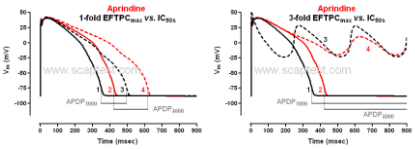


Transmural dispersion of repolarization

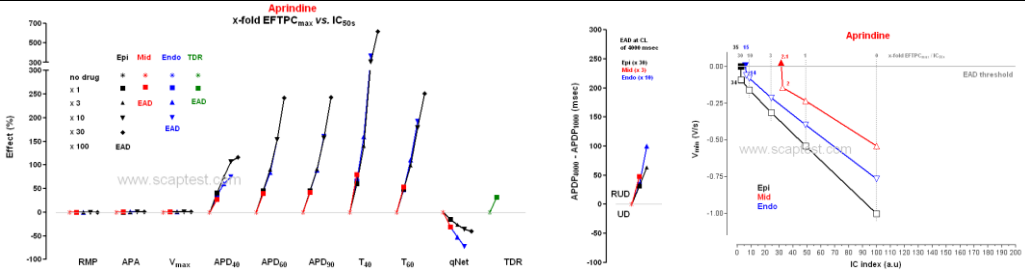


Reverse use dependence on midmyocardial myocytes

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



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2. Redfern WS et al. (2003) *Cardiovasc. Res.* **58 :** 32-45
3. Kramer J et al. (2013) *Sci.rep.* **3 :** 2100
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Abbreviations

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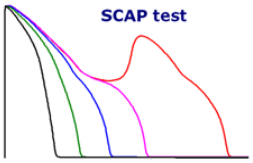

Drug	**Asenapine** 5-HT_{2a} and D_2 receptor antagonist used as antipsychotic to treat bipolar I disorder and schizophrenia

Raw data

IC_{50s} (slope) [1]	$EFTPC_{max}$ [1]	TdP risk
I_{CaL} : ---- µM (---) I_{to} : ---- µM (---) I_{Kr} : 0.3 µM (1.0) I_{NaL} : ---- µM (---) I_{Na} : ---- µM (---) I_{K1} : ---- µM (---) I_{Ks} : ---- µM (---)	0.000699 µM	Redfern [2] : not reported Kramer [3] : not reported CredibleMeds [4] : possible risk of TdP (Class 2) CiPA [5] : not reported WP [6] : 0/1 (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 = 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'

$g_j = g_{control,j}\left[1+\left(\frac{D}{IC50_j}\right)^n\right]^{-1}$ — g = maximal conductance of 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)
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where
$APD_{90}P_x$ = APD_{90} with - APD_{90} without compound at CL x

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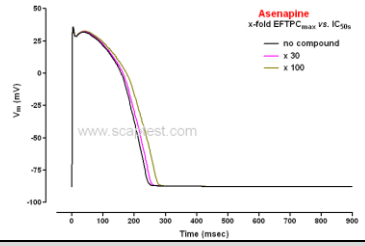
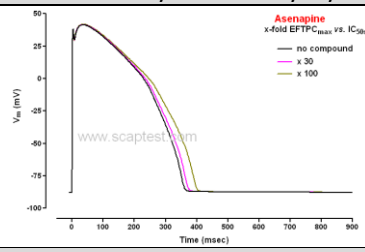
IC index = (AFKr/((AFNaL+AFCaL)/2))*100
where
AFKr, AFNaL and AFCaL = active fraction (%) of the I_{Ks}, I_{NaL} and I_{CaL}.

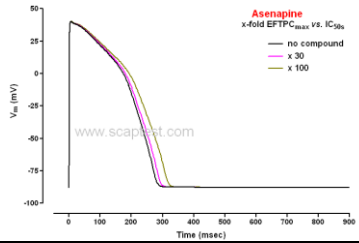
Human epicardial myocytes



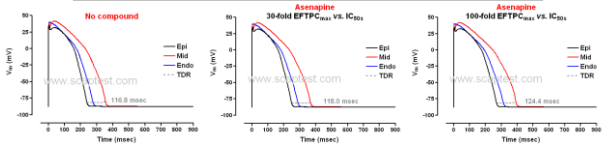
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarisation



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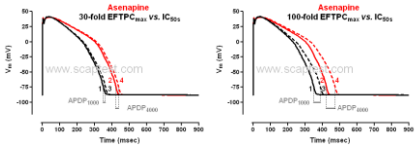
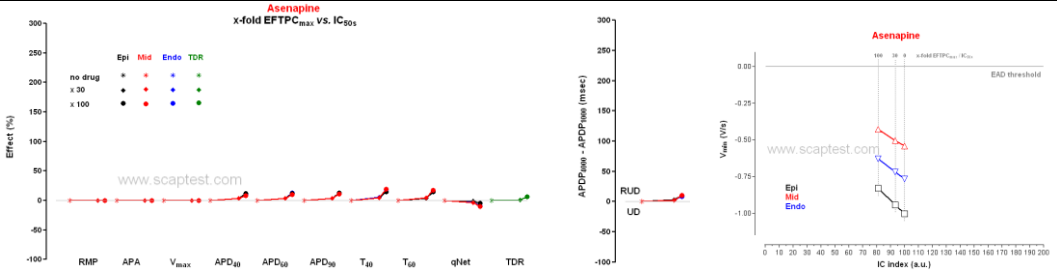
1 - CL 1000 msec without compound
2 - CL 4000 msec without compound
3 - CL 1000 msec with compound
4 - CL 4000 msec with compound



Summary



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Abbreviations

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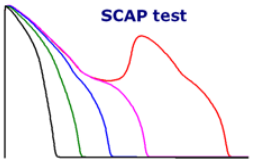

Drug	**Atomoxetine** Noradrenaline reuptake inhibitor used to treat attention deficit and hyperactivity disorder

Raw data

IC_{50s} (slope) [1]	$EFTPC_{max}$ [1]	TdP risk
I_{CaL} : ---- µM (---) I_{Kr} : 6.26 µM (0.6) I_{Na} : ---- µM (---) I_{Ks} : ---- µM (---) I_{to} : ---- µM (---) I_{NaL} : ---- µM (---) I_{K1} : ---- µM (---)	0.0178 µM	Redfern [2] : not reported Kramer [3] : not reported CredibleMeds [4] : Possible risk of TdP (Class 2) CiPA [5] : not reported WP [6] : 0/1 (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):
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- Cycle length : 1000 msec
- Beat number: 100

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O=open probability of channel 'j'
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E_{ion} = reversal potential for species of ions which flows through channel 'j'

$g_j = g_{control,j}\left[1+\left(\frac{D}{(IC50)_j}\right)^n\right]^{-1}$

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$g_{control,j}$ = drug-free maximal conductance of channel 'j'
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- 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
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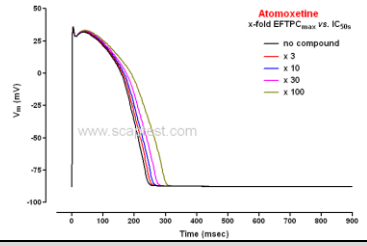
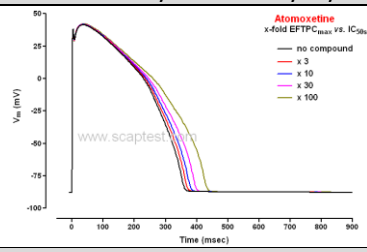
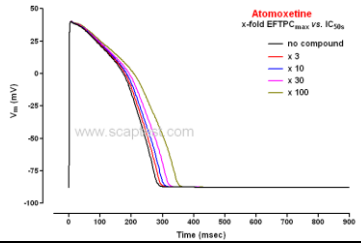
Human epicardial myocytes



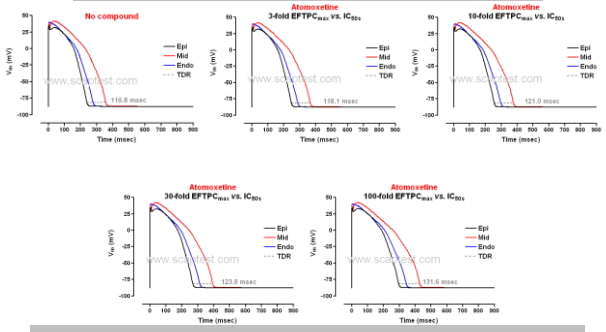
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarisation



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2 - CL 4000 msec without compound
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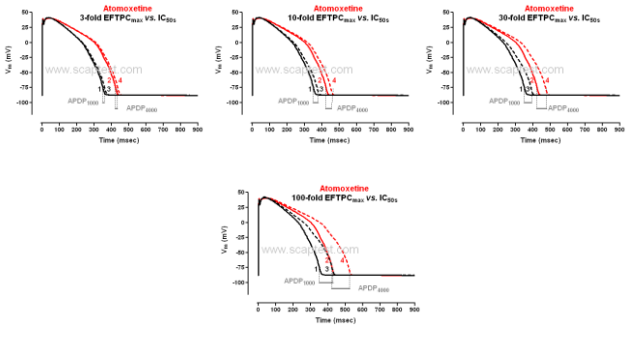
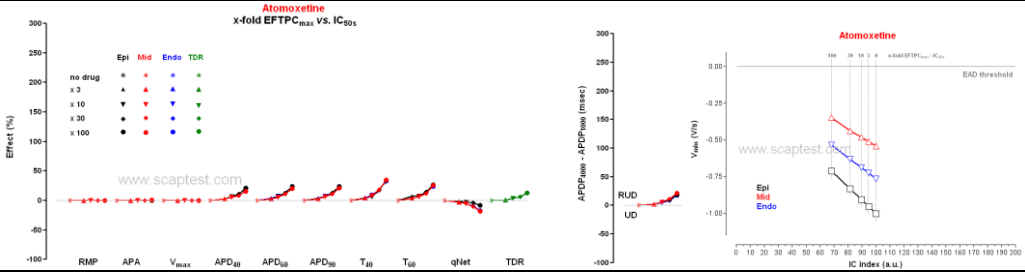


Summary



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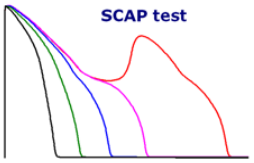

Drug

Bedaquiline

Mycobacterial ATP synthase inhibitor used to treat pulmonary multiresistant tuberculosis

Raw data

IC_{50s} (slope) [1]

I_{CaL} : ---- µM (---)
I_{to} : ---- µM (---)
I_{Kr} : 0.368 µM (0.7)
I_{NaL} : ---- µM (---)
I_{Na} : ---- µM (---)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ [1]

0.00990 µM

TdP risk

Redfern [2] : not reported
Kramer [3] : not reported
CredibleMeds [4] : possible risk of TdP (Class 2)
CiPA [5] : not reported
WP [6] : 0/1 (TdP+/TdP-)

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

g_j = maximal conductance of channel 'j'
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$g_j = g_{control,j}\left[1 + \left(\frac{D}{(IC50)_j}\right)^n\right]^{-1}$

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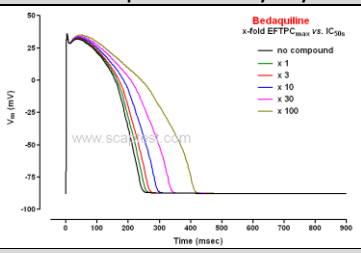
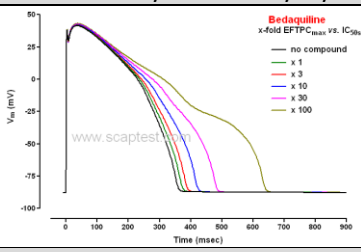
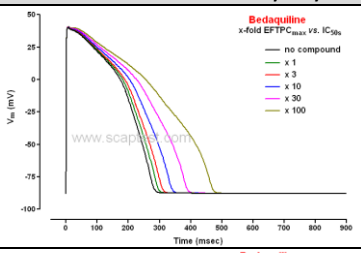
Human epicardial myocytes



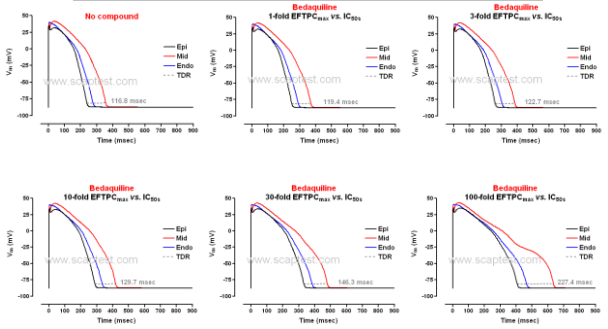
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarisation



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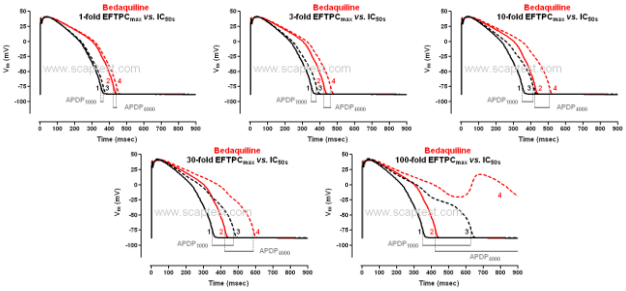
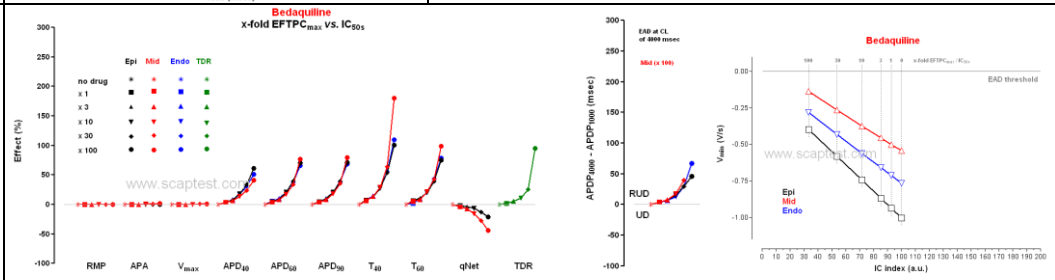


Summary



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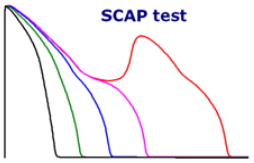

Drug

Bosutinib

Tyrosine kinase inhibitor used to treat chronic myelogenous leukemia

Raw data

IC_{50s} (slope) [1]

I_{CaL} : ---- µM (---)
I_{to} : ---- µM (---)
I_{Kr} : 0.3 µM (1.0)
I_{NaL} : ---- µM (---)
I_{Na} : ---- µM (---)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ [1]

0.0226 µM

TdP risk

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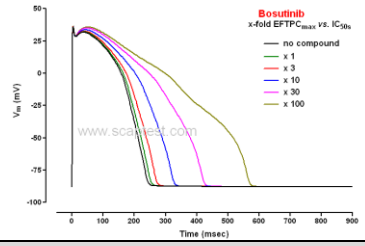
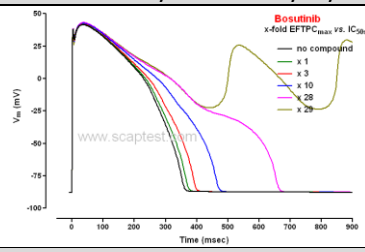
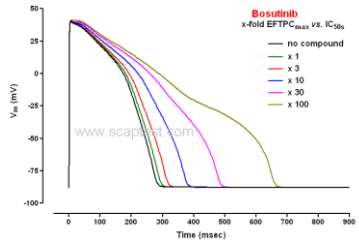


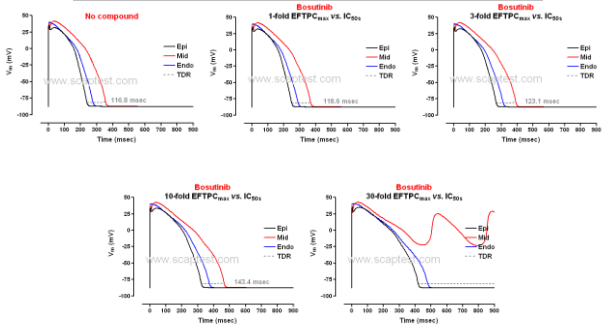
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarisation



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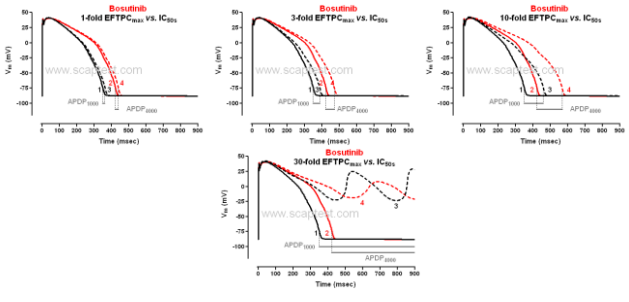
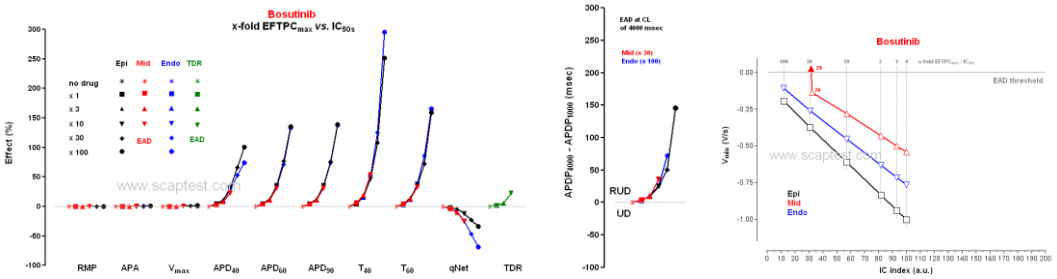


Summary



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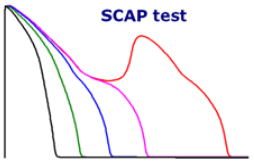
Abbreviations

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 $I_{CaL}+I_{Kr}+I_{Na}+I_{to}+I_{NaL}+I_{K1}$, **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, **V/s** : volt per second



Drug

Bupivacaine

Voltage-gated Na^+ ($Na_v1.5$) channel blocker used as local anesthetic in a wide variety of superficial and invasive procedures

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 35.481 µM (1.0)
I_{Kr} : 10.715 µM (1.0)
I_{Na} : 3.090 µM (1.0)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : 4.467 µM (1.0)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ [1]

0.260 µM

TdP risk

Redfern [2] : not reported
Kramer [3] : not reported
CredibleMeds [4] : not classified with TdP risk (class 4)
CiPA [5] : not reported
WP [6] : not reported

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
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- 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'

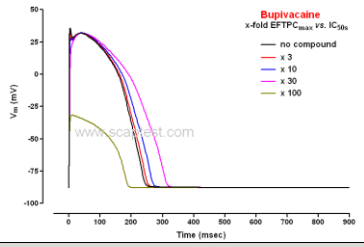
$g_j = g_{control\_j}\left[1+\left(\frac{D}{IC50_j}\right)^{n}\right]^{-1}$; g_j = maximal conductance of channel 'j' ; $G_{control\_j}$ = drug-free maximal conductance of channel 'j' ; IC50 = 50% of inhibition of a drug for channel 'j' ; D= drug concentration (EFTPC for example) ; n = hill slope

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

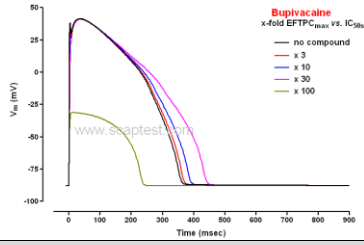
where
$APD_{90}P_x$ = APD_{90} with - APD_{90} without compound at CL x

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}

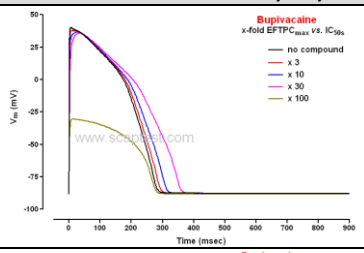
Human epicardial myocytes



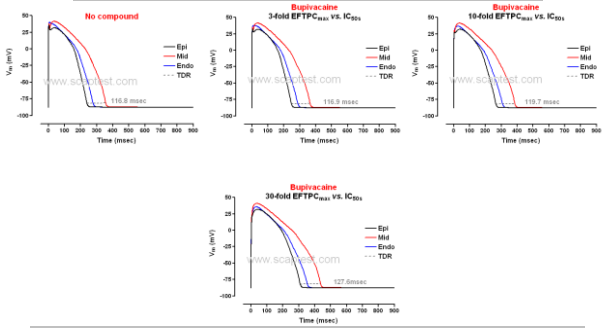
Human midmyocardial myocytes



Human endocardial myocytes

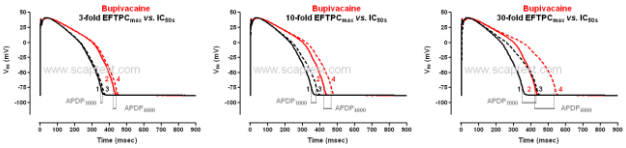


Transmural dispersion of repolarisation

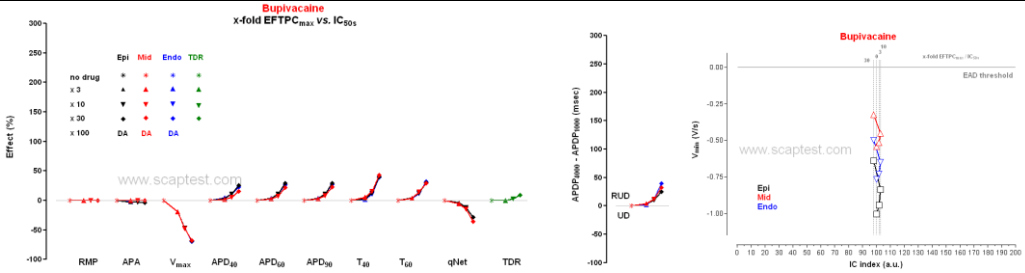


Reverse use dependence on midmyocardial myocytes

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



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1. Watt ED et al. (2022) *J.Pharmacol.Tox.Methods* **118 :** 107213
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. Wiśniowska B 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 & Crumb WJ Jr (2019) *J Pharmacol Toxicol Methods* **96 :** 15-26

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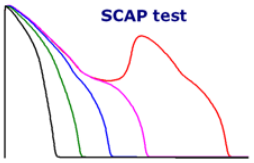

Drug

Carbamazepine

Mechanism of action not fully elucidated, used as anticonvulsant to treat various types of seizures and pain resulting from trigeminal neuralgia

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 371.5 µM (1.0) I_{to} : ---- µM (---)
I_{Kr} : ---- µM (---) I_{NaL} : 93.2 µM (1.0)
I_{Na} : 398.1µM (1.0) I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ [1]

9.481 µM

TdP risk

Redfern [2] : not reported
Kramer [3] : not reported
CredibleMeds [4] : not classified with TdP risk (class 4)
CiPA [5] : not reported
WP [6] : not reported

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'

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

g_j = maximal conductance of channel 'j'
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where
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IC index = (AFKr/((AFNaL+AFCaL)/2))*100
where
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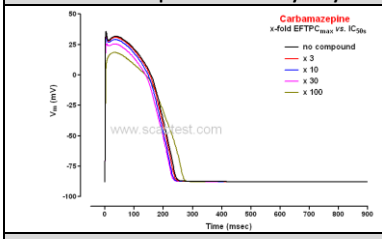
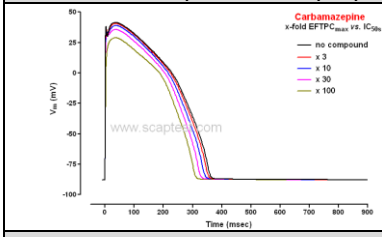
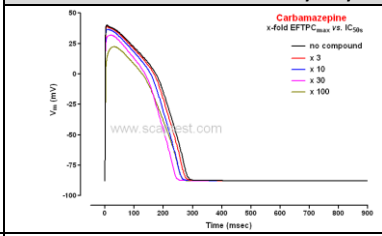
Human epicardial myocytes



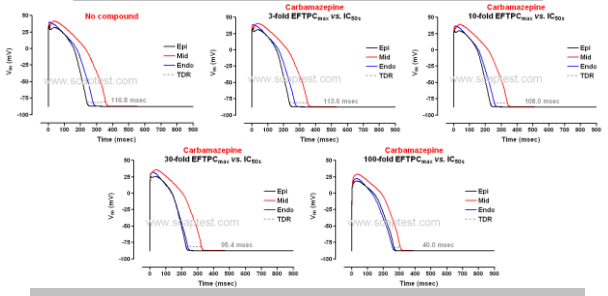
Human midmyocardial myocytes



Human endocardial myocytes

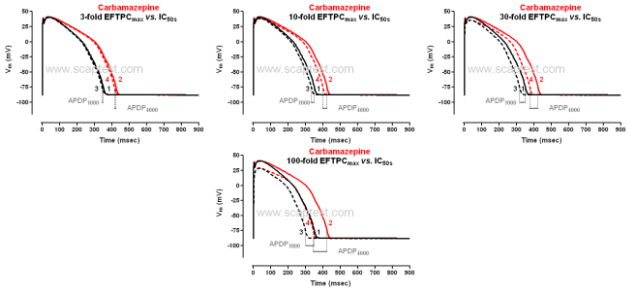


Transmural dispersion of repolarisation



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



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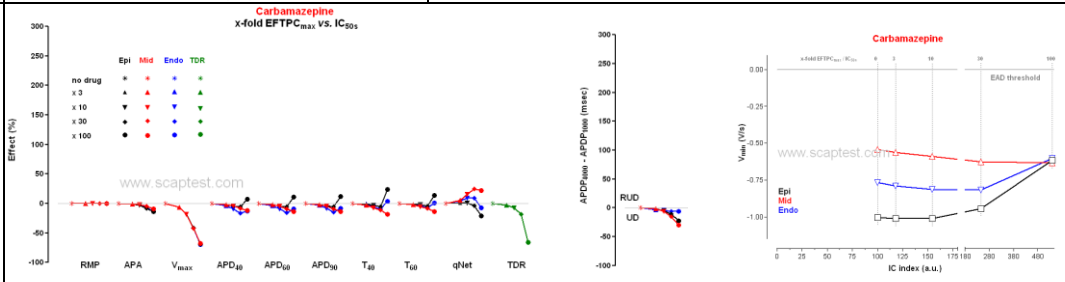

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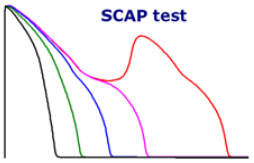

Drug

Carvedilol

Non-selective β-adrenergic antagonist used to treat mild to severe heart failure, hypertension or left ventricular dysfunction following myocardial infarction in clinically stable patients

Raw data

IC_{50s} (slope) (1)

I_{CaL} : ---- µM (---)
I_{to} : ---- µM (---)
I_{Kr} : 0.51 µM (0.8)
I_{NaL} : ---- µM (---)
I_{Na} : ---- µM (---)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$

0.005117 µM

Gehr TW et al. (1999)
Eur. J. Clin. Pharmacol. **55** : 269-277

TdP risk

Redfern (2) : not reported
Kramer (3) : not reported
CredibleMeds (4) : not classified with TdP risk (class 4)
CiPA (5) : not reported
WP (6) : not reported

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}

$I_j = g_j O (V - E_{ion})$; $g_j = g_{control,j}\left[1+\left(\frac{D}{[IC50]_j}\right)^{n_j}\right]^{-1}$

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O=open probability of channel 'j'
V= voltage membrane
E_{ion}= reversal potential for species of ions which flows through channel 'j'
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where
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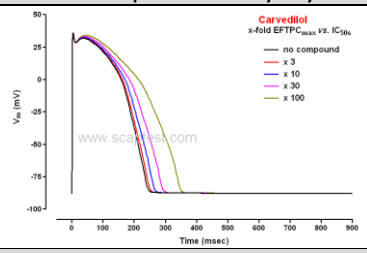
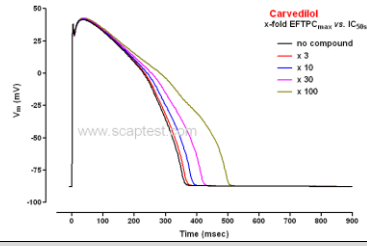
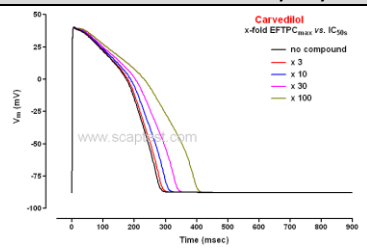
Human epicardial myocytes



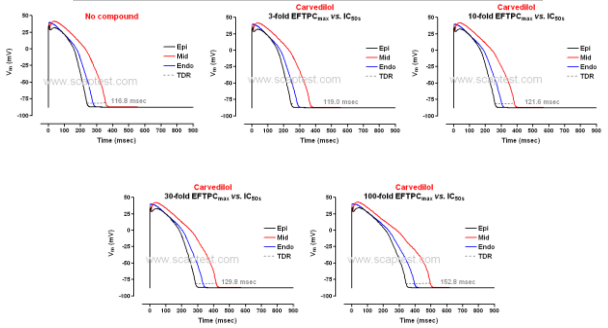
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarization



Reverse use dependence on midmyocardial myocytes

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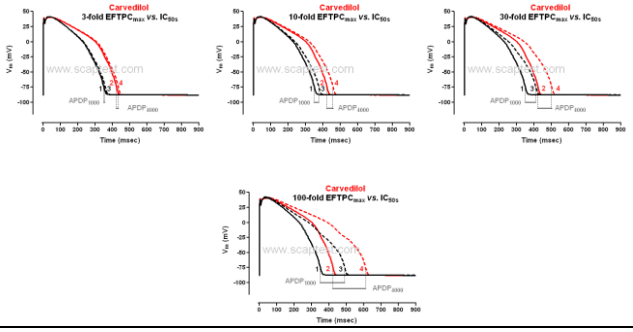
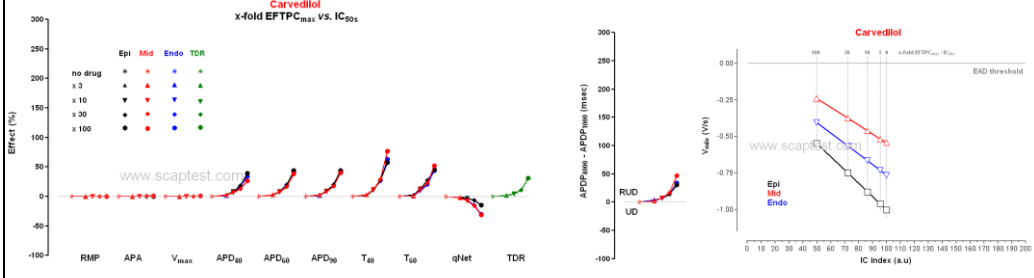


Summary



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2. Redfern WS et al. (2003) *Cardiovasc. Res.* **58** : 32-45
3. Kramer J et al. (2013) *Sci.rep.* **3** : 2100
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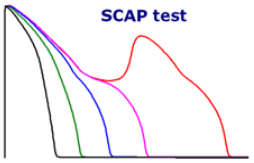

Drug	**Ceritinib** Anaplastic lymphoma kinase (ALK) inhibitor used to treat ALK positive metastatic non-small cell lung cancer (NSCLC)

Raw data

IC_{50s} (slope) [1]	$EFTPC_{max}$ [1]	TdP risk
I_{CaL} : ---- µM (---) I_{to} : ---- µM (---) I_{Kr} : 0.4 µM (1.0) I_{NaL} : ---- µM (---) I_{Na} : ---- µM (---) I_{K1} : ---- µM (---) I_{Ks} : ---- µM (---)	0.058 µM	Redfern [2] : not reported Kramer [3] : not reported CredibleMeds [4] : Possible risk of TdP (class 2) CiPA [5] : not reported WP [6] : 0/1 (TdP+ / TdP-)

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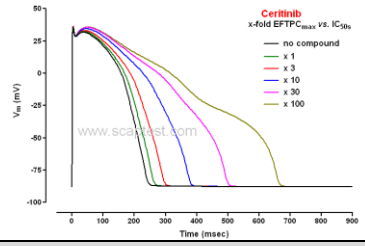
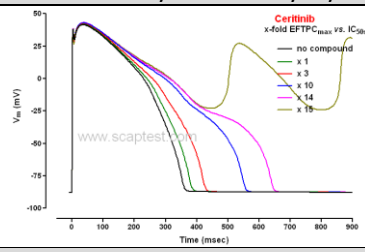
IC index = (AFKr/((AFNaL+AFCaL)/2))*100
where
AFKr, AFNaL and AFCaL = active fraction (%) of the I_{Ks}, I_{NaL} and I_{CaL}.

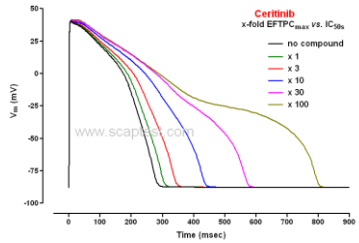
Human epicardial myocytes



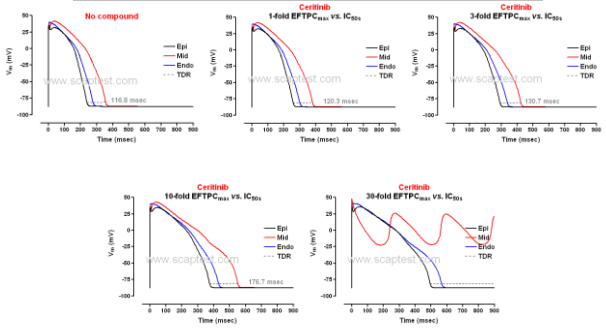
Human midmyocardial myocytes



Human endocardial myocytes

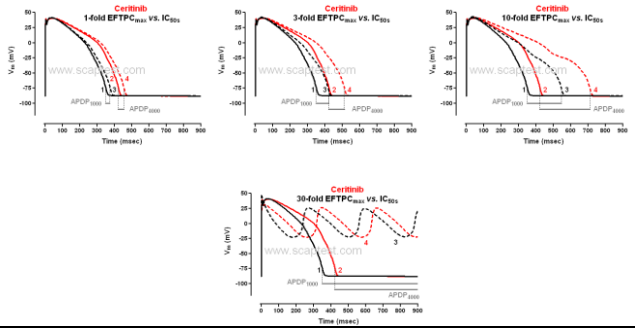


Transmural dispersion of repolarization

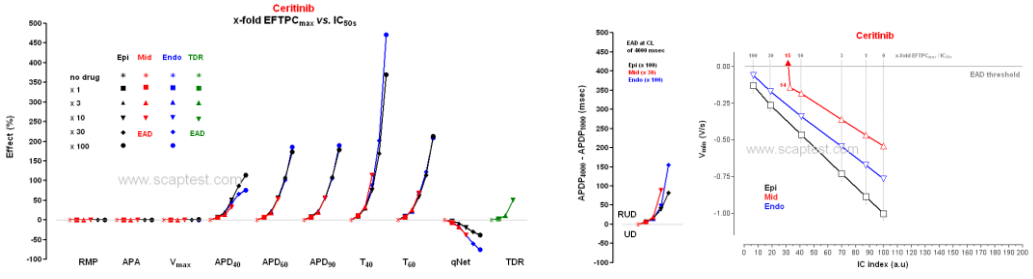


Reverse use dependence on midmyocardial myocytes

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



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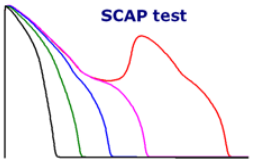
2. Redfern WS et al. (2003) *Cardiovasc. Res.* **58** : 32-45
3. Kramer J et al. (2013) *Sci.rep.* **3** : 2100
4. Woosley RL (2015) www.CredibleMeds.org
5. CiPA (2016) www.ilsiextra.org/hesi/science/cardiac/cipa/Project
6. Wiśniowska B et al. (2017) *Drug discovery today* **22** : 10-16
7. O'Hara T et al. (2011) *PLoS Comput. Biol.* **7** : e1002061.8
8. Mirams GR et al. (2011) *Cardiovasc. Res.* **91** : 53-61
9. Christophe B & 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_{Kr}+I_{Na}+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, **V/s** : volt per second



Drug	**Clomipramine** 5-HT reuptake inhibitor used as antidepressant to treat obsessive-compulsive disorders

Raw data

IC_{50s} (slope) [1]		$EFTPC_{max}$ [1]	TdP risk
I_{CaL} : 15.3 µM (1.0)	I_{to} : ---- µM (---)	0.00584 µM	Redfern [2] : not reported
I_{Kr} : 0.13 µM (0.43)	I_{NaL} : ---- µM (---)		Kramer [3] : not reported
I_{Na} : 2.6 µM (1.0)	I_{K1} : ---- µM (---)		CredibleMeds [4] : conditional risk of TdP (class 3)
I_{Ks} : ---- µM (---)			CiPA [5] : not reported
			WP [6] : 2/1 (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'

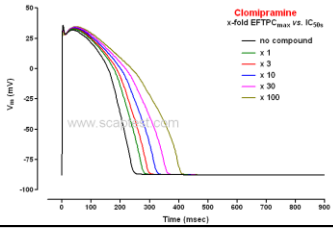
$g_j = g_{control,j}\left[1+\left(\frac{D}{IC50_j}\right)^n\right]^{-1}$ — g_j = maximal conductance of channel 'j', $g_{control,j}$ = drug-free maximal conductance of channel 'j', IC50 = 50% of inhibition of a drug for channel 'j', D= drug concentration (EFTPC for example), n = hill slope

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

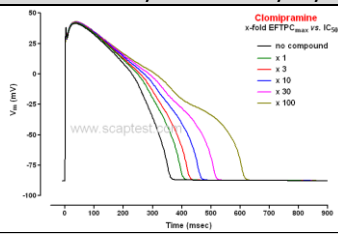
where
$APD_{90}P_x$ = APD_{90} with - APD_{90} without compound at CL x

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

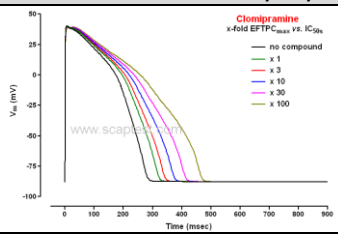
Human epicardial myocytes



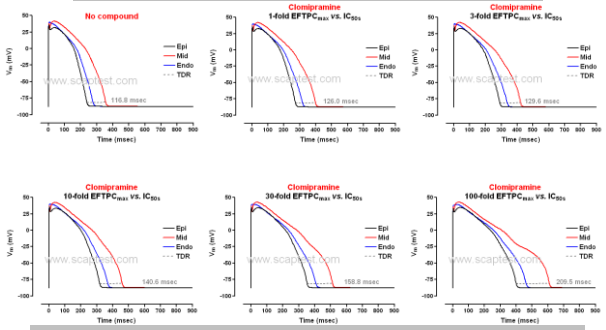
Human midmyocardial myocytes



Human endocardial myocytes

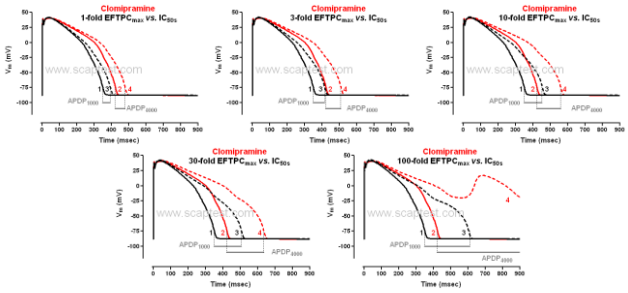


Transmural dispersion of repolarisation

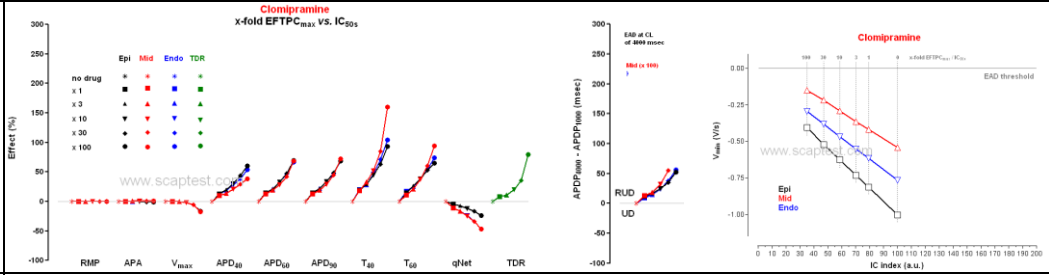


Reverse use dependence on midmyocardial myocytes

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



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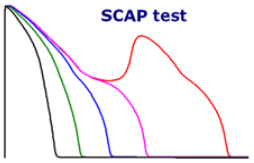
Abbreviations

AP : action potential, **APA** : AP amplitude, $\mathbf{APD_{40,60\ or\ 90}}$: 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, $\mathbf{IC_{50}}$: 50% inhibition concentration, **mid** : midmyocardial myocyte, **msec** : millisecond, **mV** : millivolt, **qNet** : integration sum of I_{CaL}+I_{Kr}+I_{Ks}+I_{to}+I_{NaL}+I_{K1}, **RMP** : resting membrane potential, **RUD** : reverse use dependence, $\mathbf{T_{40,60}}$: APD_{90}-APD_{40} or APD_{60} (~triangulation), **TdP** : torsade de pointes , **TDR** : transmural dispersion of repolarization, $\mathbf{V_m}$: membrane voltage, $\mathbf{V_{max}}$: maximal rate of AP rise , $\mathbf{V_{min}}$: minimal rate of AP decrease at EAD take-off voltage, **V/s** : volt per second



Drug

Crizotinib

Tyrosine kinase inhibitor used to treat metastatic non-small cell lung cancer

Raw data

IC_{50s} (slope) [1]

I_{CaL} : ---- µM (---)
I_{to} : ---- µM (---)
I_{Kr} : 8.9 µM (1.0)
I_{NaL} : ---- µM (---)
I_{Na} : ---- µM (---)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ [1]

0.01991 µM

TdP risk

Redfern [2] : not reported
Kramer [3] : not reported
CredibleMeds [4] : possible risk of TdP (Class 2)
CiPA [5] : not reported
WP [6] : 0/1 (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 = 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'

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

g = maximal conductance of channel 'j'
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IC50 = 50% of inhibition of a drug for channel 'j'
D= drug concentration (EFTPC for example)
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TDR and RUD estimation:
- TDR = APD_{90} mid - APD_{90} epi (at CL of 1000 msec)
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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
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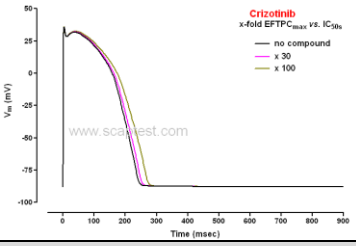
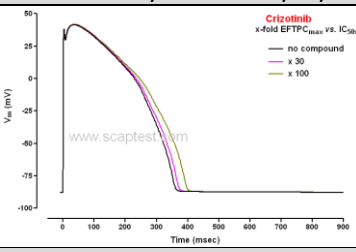
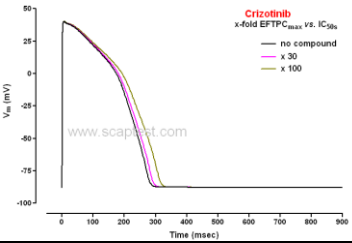
Human epicardial myocytes



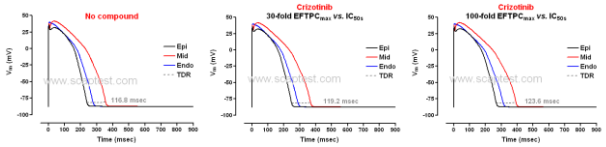
Human midmyocardial myocytes



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
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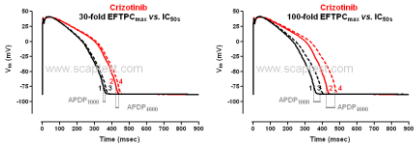
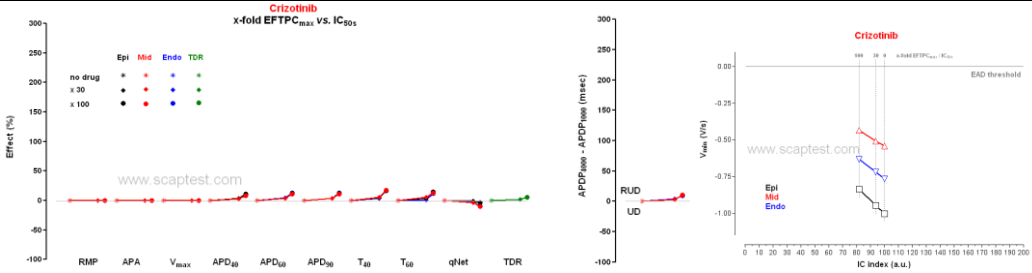
4 - CL 4000 msec with compound



Summary



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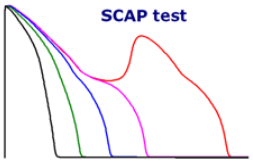

Drug

Dasabuvir

Direct-acting antiviral agent used to treat specific hepatitis C virus infections in combination with other antiviral agents

Raw data

IC_{50s} (slope) [1]

I_{CaL} : ---- µM (---)
I_{to} : ---- µM (---)
I_{Kr} : 3.2 µM (1.0)
I_{NaL} : ---- µM (---)
I_{Na} : ---- µM (---)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ [1]

0.001 µM

TdP risk

Redfern [2] : not reported
Kramer [3] : not reported
CredibleMeds [4] : not classified with TdP risk (class 4)
CiPA [5] : not reported
WP [6] : not reported

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

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

g_j = maximal conductance of channel 'j'
O=open probability of channel 'j'
V= voltage membrane
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$g_j = g_{j\,control,j}\left[1+\left(\frac{D}{IC50_j}\right)^n\right]^{-1}$

$g_{j\,control,j}$= drug-free maximal conductance of channel 'j'
IC50 = 50% of inhibition of a drug for channel 'j'
D= drug concentration (EFTPC for example)
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TDR and RUD estimation:

- TDR = APD_{90} mid - APD_{90} epi (at CL of 1000 msec)
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where
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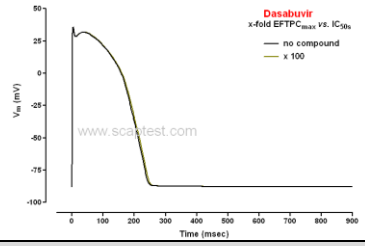
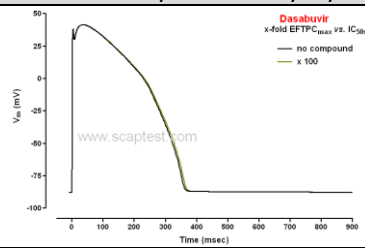
IC index calculation [9]:

IC index = (AFKr/((AFNaL+AFCaL)/2))*100
where
AFKr, AFNaL and AFCaL = active fraction (%) of the I_{Ks}, I_{NaL} and I_{CaL}

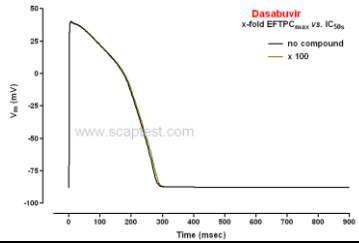
Human epicardial myocytes



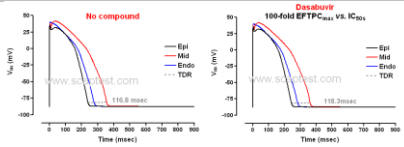
Human midmyocardial myocytes



Human endocardial myocytes

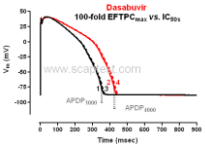


Transmural dispersion of repolarization

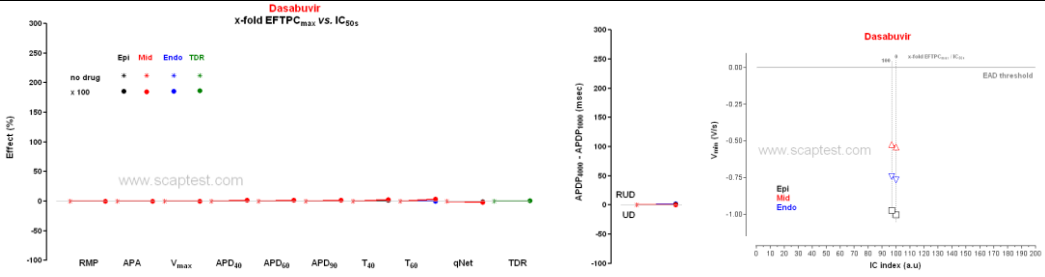


Reverse use dependence on midmyocardial myocytes

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



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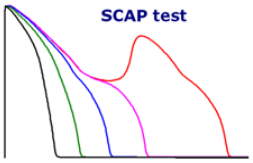
9. Christophe B & Crumb WJ Jr (2019) *J Pharmacol Toxicol Methods* **96** : 15-26

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_{Kr}+I_{Na}+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, **V/s** : volt per second



Drug

Digoxin

Na-K ATP$_{ase}$ inhibitor used to treat mild to moderate heart failure or to control ventricular response rate in chronic atrial fibrillation

Raw data

IC_{50s} (slope) [1]

I_{CaL} : ---- µM (---)
I_{to} : ---- µM (---)
I_{Kr} : 0.054 µM (1.0)
I_{NaL} : ---- µM (---)
I_{Na} : ---- µM (---)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ [1]

0.00127 µM

TdP risk

Redfern [2] : not reported
Kramer [3] : not reported
CredibleMeds [4] : not classified with TdP risk (class 4)
CiPA [5] : not reported
WP [6] : 1/0 (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'

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

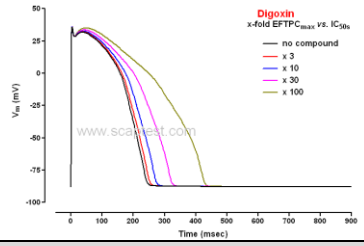
$g_{control,j}$= drug-free maximal conductance of channel 'j'
IC50 = 50% of inhibition of a drug for channel 'j'
D= drug concentration (EFTPC for example)
n = hill slope

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

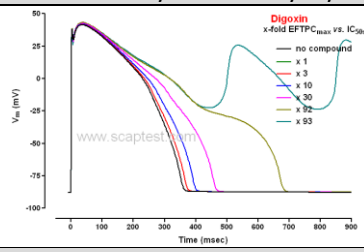
where
$APD_{90}P_x$ = APD_{90} with - APD_{90} without compound at CL x

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

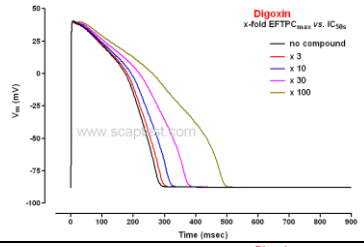
Human epicardial myocytes



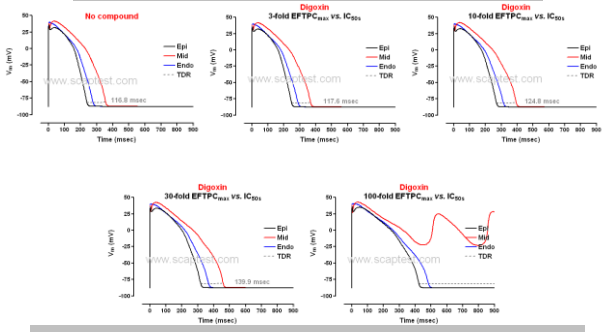
Human midmyocardial myocytes



Human endocardial myocytes

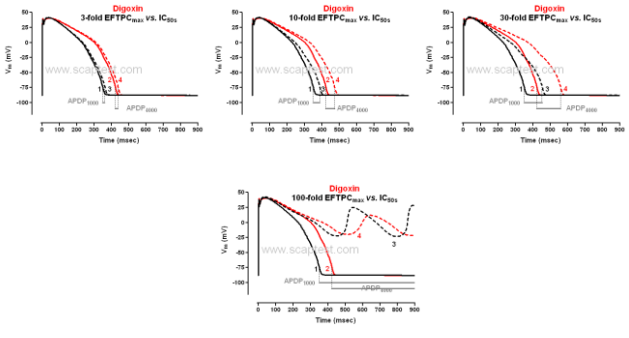


Transmural dispersion of repolarisation

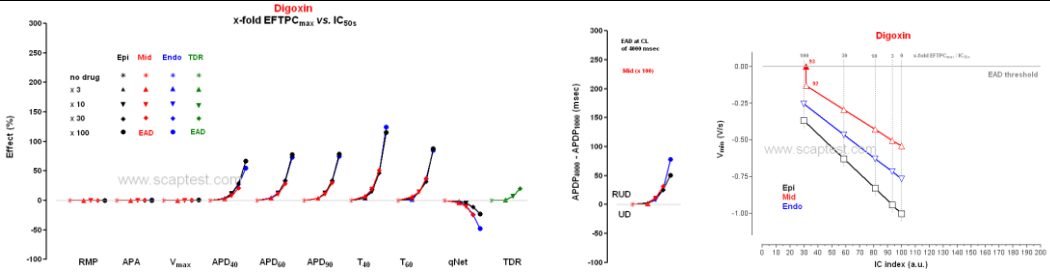


Reverse use dependence on midmyocardial myocytes

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



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1. www.tox-portal.com and www.go.drugbank.com
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. Wisnioswska B 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
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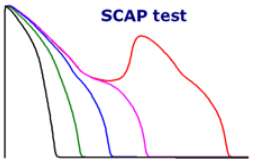

Drug

Doxepin

Noradrenaline and serotonin reuptake inhibitor used to treat depression, anxiety, manic-depressive disorder and insomnia

Raw data

IC_{50s} (slope) [1]

I_{CaL} : ---- µM (---)
I_{to} : ---- µM (---)
I_{Kr} : 2.14 µM (1.0)
I_{NaL} : ---- µM (---)
I_{Na} : ---- µM (---)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ [1]

0.013996 µM

TdP risk

Redfern [2] : isolated TdP reports (class 4)
Kramer [3] : not reported
CredibleMeds [4] : conditional risk of TdP (class 3)
CiPA [5] : not reported
WP [6] : 4/1 (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}

$I_j = g_j O (V - E_{ion})$; $g_j = g_{control,j}\left[1+\left(\frac{D}{(IC50)_j}\right)^n\right]^{-1}$

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'
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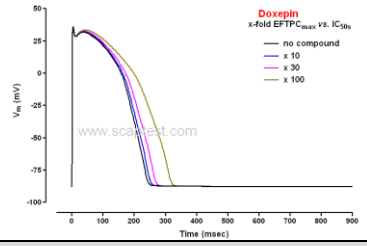
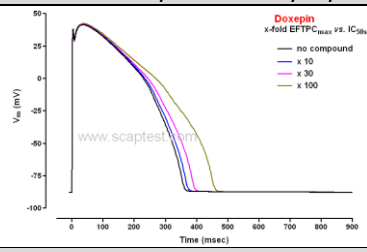
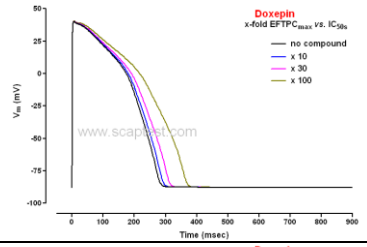
Human epicardial myocytes



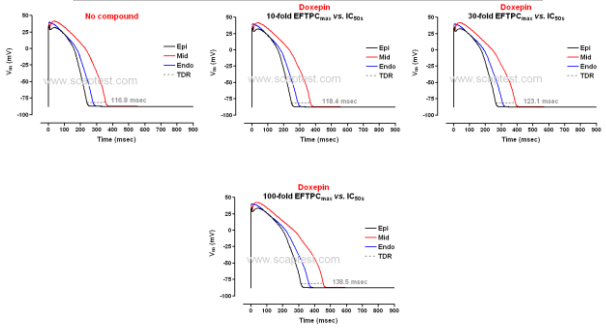
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarization



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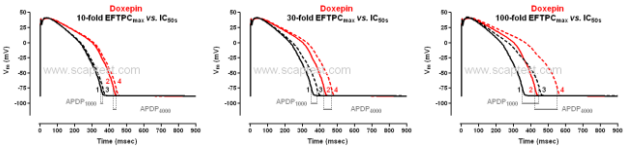

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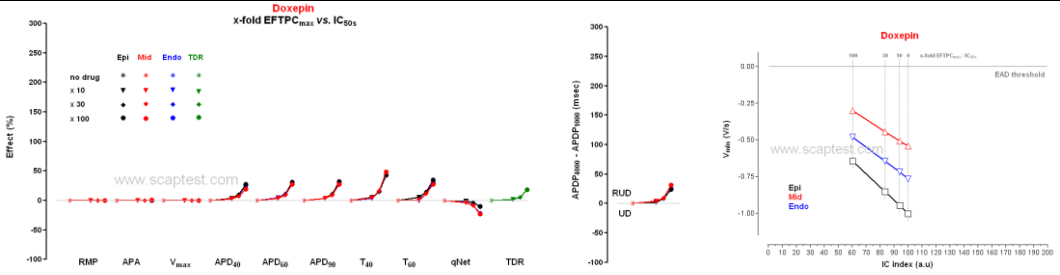

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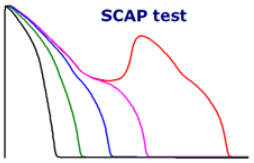

Drug

Felodipine

Voltage-gated L-type Ca^{++} channel ($Ca_v1.2$) blocker used to treat hypertension

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 0.012 µM (1.0)
I_{to} : ---- µM (---)
I_{Kr} : 8.128 µM (1.0)
I_{NaL} : 0.437 µM (1.0)
I_{Na} : 8.511 µM (1.0)
I_{K1} : ---- µM (---)
I_{KS} : ---- µM (---)

$EFTPC_{max}$ [1]

0.0003 µM

TdP risk

Redfern [2] : not reported
Kramer [3] : not reported
CredibleMeds [4] : not classified with TdP risk (class 4)
CiPA [5] : not reported
WP [6] : not reported

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):
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- Cycle length : 1000 msec
- Beat number: 100

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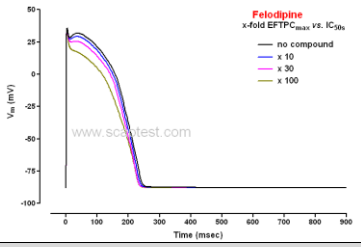
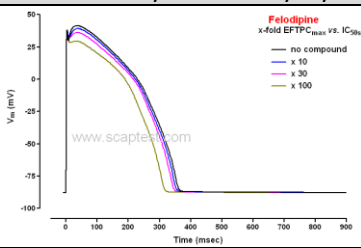
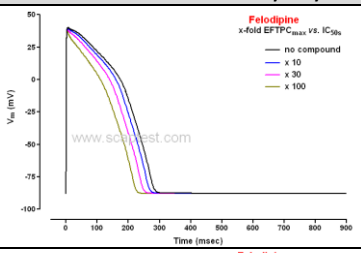
Human epicardial myocytes



Human midmyocardial myocytes



Human endocardial myocytes



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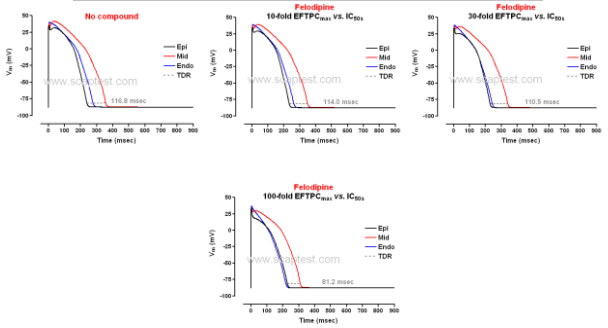

Reverse use dependence on midmyocardial myocytes

1 - CL 1000 msec without compound
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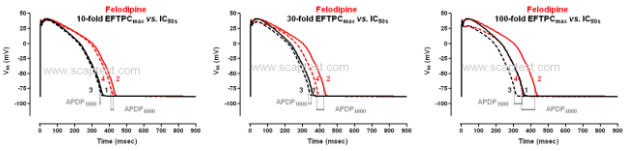
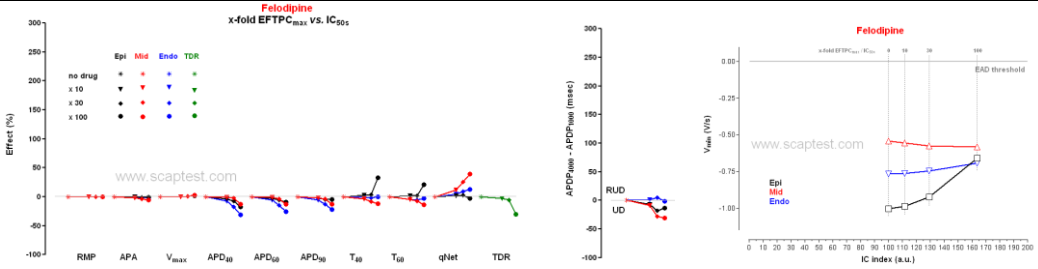


Summary



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2. Redfern WS et al. (2003) *Cardiovasc. Res.* **58 :** 32-45
3. Kramer J et al. (2013) *Sci.rep.* **3 :** 2100
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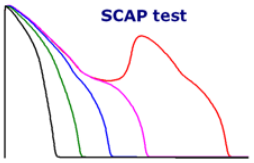

Drug

Fenspiride

Histamine H_1 antagonist and phosphodiesterase ($PDE_{3,\ 4\ and\ 5}$) inhibitor used to treat respiratory diseases
no longer marketed in Europe (1)

Raw data

IC_{50s} (slope) (1)

I_{CaL} : ---- µM (---)
I_{Kr} : 15.14 µM (1.0)
I_{Na} : ---- µM (---)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$

0.7121 µM

Montes B et al. (1993)
Eur J Clin Pharmacol. **45** : 169-172

TdP risk

Redfern (2) : not reported
Kramer (3) : not reported
CredibleMeds (4) : not reported
CiPA (5) : not reported
WP (6) : not reported

Results

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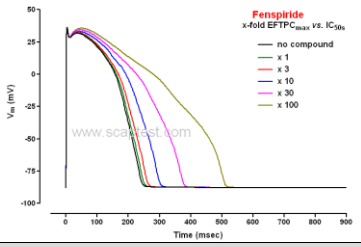
- RUD = $APD_{90}P_{4000}$-$APD_{90}P_{1000}$

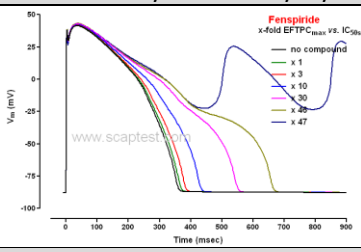
where
$APD_{90}P_x$ = APD_{90} with - APD_{90} without compound at CL x

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}

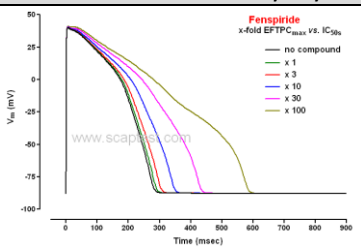
Human epicardial myocytes



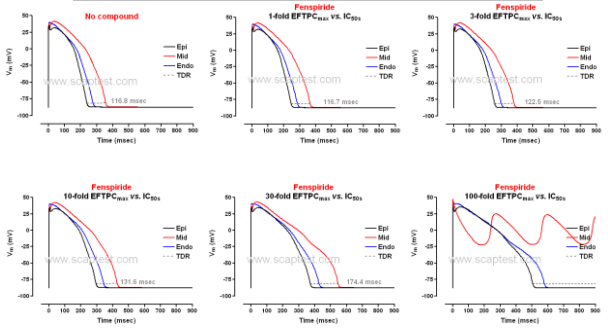
Human midmyocardial myocytes



Human endocardial myocytes

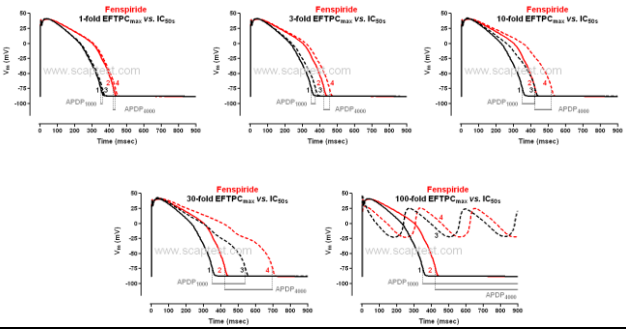


Transmural dispersion of repolarization

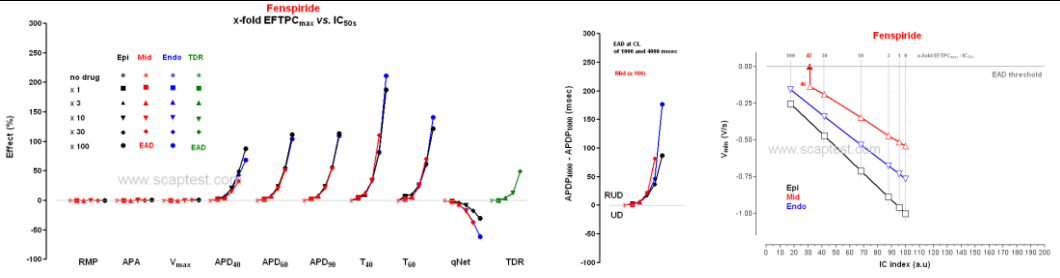


Reverse use dependence on midmyocardial myocytes

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



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3. Kramer J et al. (2013) *Sci.rep.* **3** : 2100
4. Woosley RL (2015) www.CredibleMeds.org
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Abbreviations

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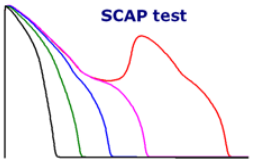

Drug

Fluconazole

Lanosterol 14-α-demethylase enzyme inhibitor used to treat various fungal infections including candidiasis

Raw data

IC_{50s} (slope) [1]

I_{CaL} : ---- µM (---)
I_{Kr} : 48.2 µM (0.32)
I_{Na} : ---- µM (---)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ [1]

87.9222 µM

TdP risk

Redfern [2] : not reported
Kramer [3] : not reported
CredibleMeds [4] : known risk of TdP (Class 1)
CiPA [5] : not reported
WP [6] : 3/1 (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 = 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'

$g_j = g_{control,j}\left[1+\left(\frac{D}{(IC50)_j}\right)^n\right]^{-1}$

$g_{control,j}$= 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
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IC index calculation [9]:

IC index = (AFKr/((AFNaL+AFCaL)/2))*100
where
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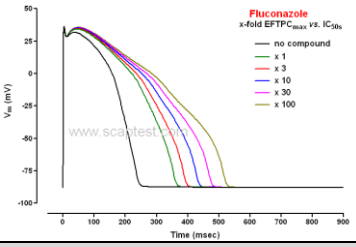
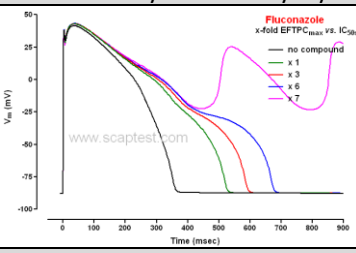
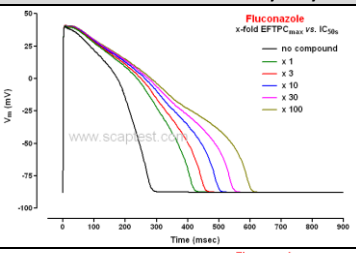
Human epicardial myocytes



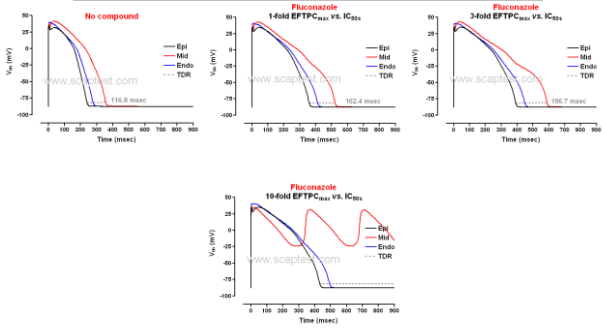
Human midmyocardial myocytes



Human endocardial myocytes

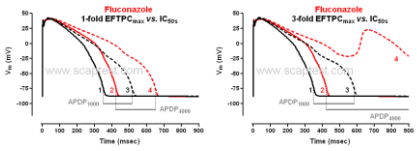


Transmural dispersion of repolarisation

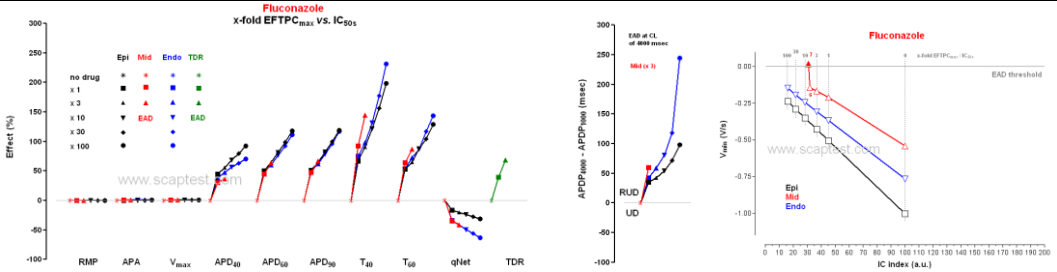


Reverse use dependence on midmyocardial myocytes

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



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6. Wisnioswska B et al. (2017) *Drug discovery today* **22 :** 10-16
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9. Christophe B et al. (2019) *J Pharmacol Toxicol Methods* **96 :** 15-26

Abbreviations

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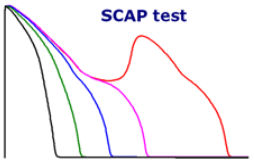

Drug

Furosemide

Sodium-potassium-chloride (NKCC1 and NKCC2) cotransporter inhibitor used to treat hypertension and edema in congestive heart failure, liver cirrhosis, renal disease and hypertension

Raw data

IC_{50s} (slope) (1)

I_{CaL} : ---- µM (---)
I_{to} : ---- µM (---)
I_{Kr} : 25.5 µM (1.0)
I_{NaL} : ---- µM (---)
I_{Na} : ---- µM (---)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ (1)

0.23927 µM

Bragatto MS (2011) *J. Bioequiv. Availab.* **3**: 191-197

TdP risk

Redfern (2) : isolated report of TdP (class 4)
Kramer (3) : not reported
CredibleMeds (4) : conditional risk of TdP (class 3)
CiPA (5) : not reported
WP (6) : 1/2 (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'

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

g = maximal conductance of channel 'j'
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IC index = (AFKr/((AFNaL+AFCaL)/2))*100
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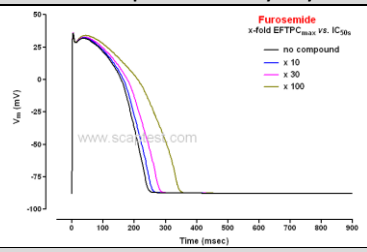
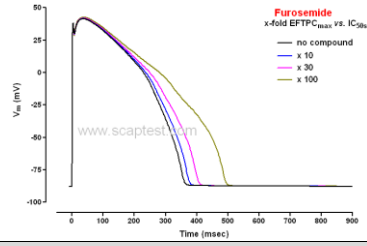
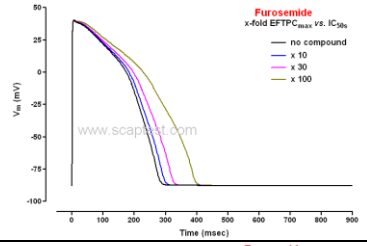
Human epicardial myocytes



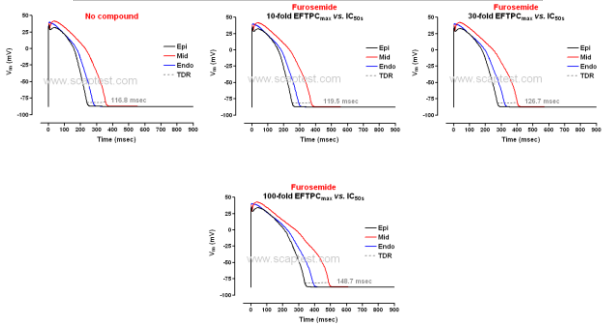
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarization



Reverse use dependence on midmyocardial myocytes

1 - CL 1000 msec without compound
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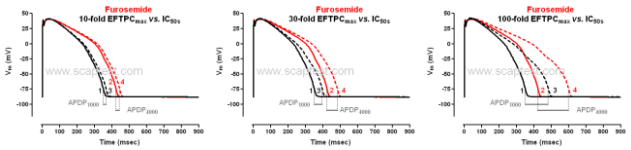
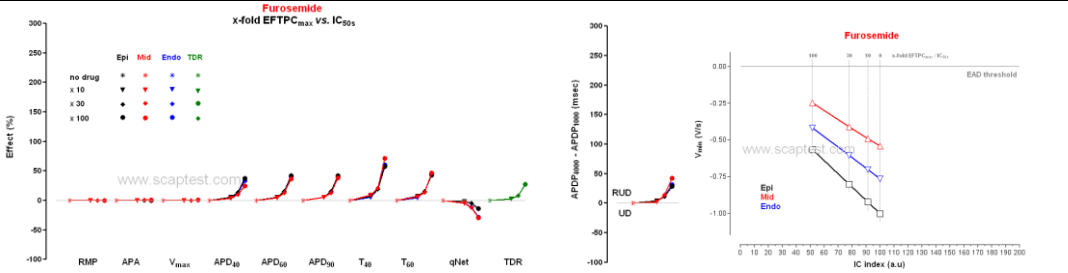


Summary



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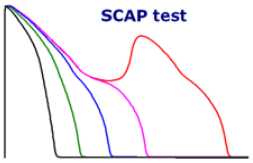

Drug	**Galantamine** Acetylcholinesterase inhibitor used to treat mild to moderate dementia of Alzheimer's type

Raw data

IC_{50s} (slope) [1]	$EFTPC_{max}$ [1]	TdP risk
I_{CaL} : ---- µM (---) I_{to} : ---- µM (---) I_{Kr} : 760.0 µM (1.0) I_{NaL} : ---- µM (---) I_{Na} : ---- µM (---) I_{K1} : ---- µM (---) I_{Ks} : ---- µM (---)	0.0291 µM	Redfern [2] : not reported Kramer [3] : not reported CredibleMeds [4] : conditional risk of TdP (class 3) CiPA [5] : not reported WP [6] : 1/0 (TdP+/TdP-)

Results

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g_j = maximal conductance of channel 'j'
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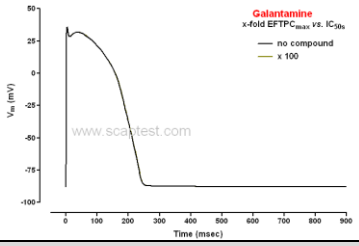
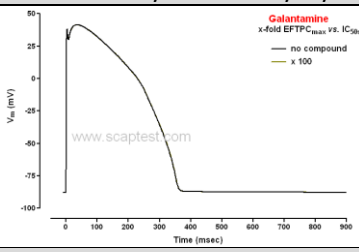
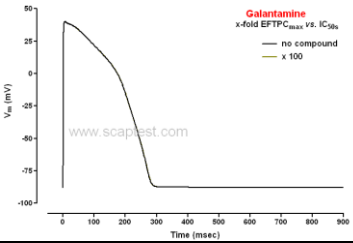
Human epicardial myocytes



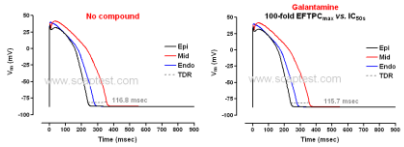
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarisation



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1 - CL 1000 msec without compound
2 - CL 4000 msec without compound
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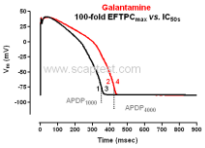
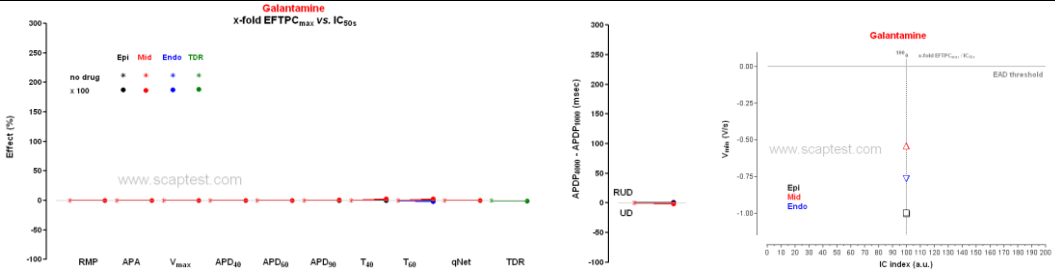


Summary



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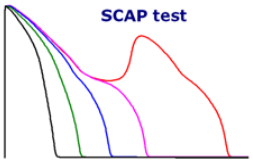
7. O'Hara T et al. (2011) *PLoS Comput. Biol.* **7**: e1002061 8
8. Mirams GR et al. (2011) *Cardiovasc. Res.* **91**: 53-61
9. Christophe B et al. (2019) *J Pharmacol Toxicol Methods* **96** : 15-26

Abbreviations

AP : action potential, **APA** : AP amplitude, **$APD_{40, 60 or 90}$** : AP duration at 40, 60 or 90 % of APA, **APDP** : APD prolongation, **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_{Kr}+I_{Na}+I_{to}+I_{NaL}+I_{K1}, **RMP** : resting membrane potential, **RUD** : reverse use dependence, **$T_{40,60}$** : APD_{90}-APD_{40} or APD_{90} ("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



Drug

Granisetron

5-HT_3-receptor antagonist used to treat nausea and vomiting in cancer therapy and postoperatively

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 2.6 µM (1.0)
I_{to} : ---- µM (---)
I_{Kr} : 3.73 µM (1.0)
I_{NaL} : ---- µM (---)
I_{Na} : ---- µM (---)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ [1]

0.00831 µM

TdP risk

Redfern [2] : not reported
Kramer [3] : not reported
CredibleMeds [4] : possible risk of TdP (Class 2)
CiPA [5] : not reported
WP [6] : 1/1 (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}

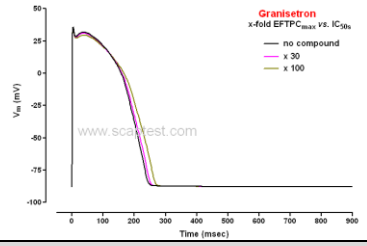
$I_j = g_j O (V - E_{ion})$; $g_j = g_{j\,control,j}\left[1+\left(\frac{D}{IC50_j}\right)^n\right]^{-1}$

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

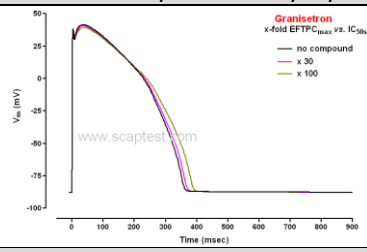
where
$APD_{90}P_x$ = APD_{90} with - APD_{90} without compound at CL x

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

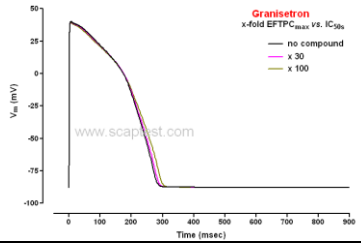
Human epicardial myocytes



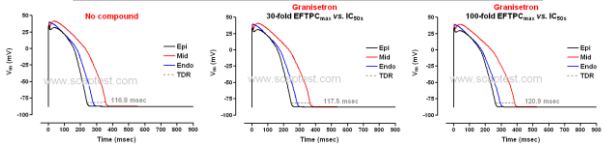
Human midmyocardial myocytes



Human endocardial myocytes

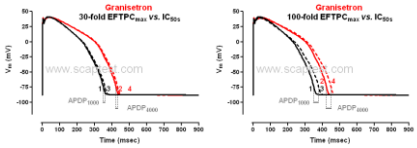


Transmural dispersion of repolarisation

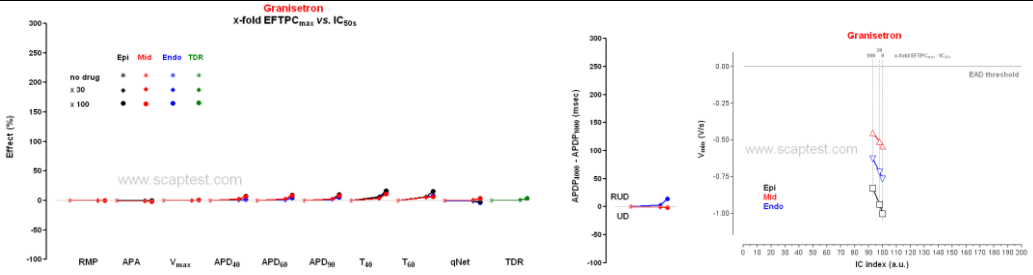


Reverse use dependence on midmyocardial myocytes

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



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4. Woosley RL (2015) www.CredibleMeds.org
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8. Mirams GR et al. (2011) *Cardiovasc. Res.* **91**: 53-61
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Abbreviations

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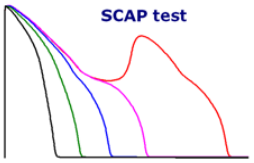

Drug

Grepafloxacin

Fluoroquinolone antibiotic used to treat various gram positive and gram negative bacterial infections
no longer marketed worldwide (Onakpoya et al (2016) *BMC Med.* **14**: 10)

Raw data

IC_{50s} (slope) (1)

I_{CaL} : ---- µM (---)
I_{Kr} : 50.00 µM (1.13)
I_{Na} : ---- µM (---)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ (1)

2.754 µM

(Lusbasch et al (2000) *Antimicrob Agents Chemother* **44**: 2600-2603)

TdP risk

Redfern (2) : unacceptable TdP risk (class 2)
Kramer (3) : not reported
CredibleMeds (4) : known risk of TdP (class 1)
CiPA (5) : not reported
WP (6) : 6/0 (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 = 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')

$g_j = g_{control\_j}\left[1+\left(\frac{D}{IC50_j}\right)^n\right]^{-1}$ (g = maximal conductance of 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)
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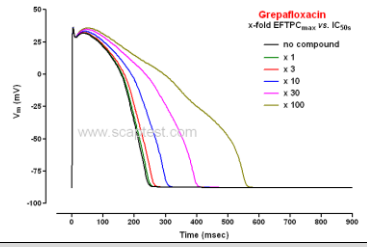
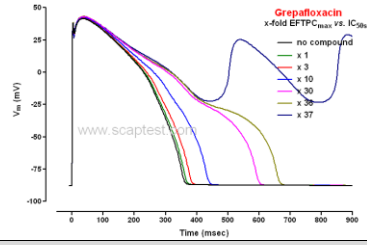
IC index calculation (9):
IC index = (AFKr/((AFNaL+AFCaL)/2))*100
where
AFKr, AFNaL and AFCaL = active fraction (%) of the I_{Kr}, I_{NaL} and I_{CaL}

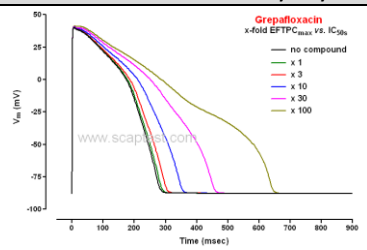
Human epicardial myocytes



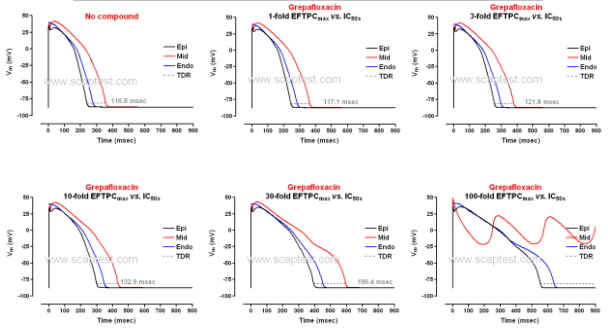
Human midmyocardial myocytes



Human endocardial myocytes

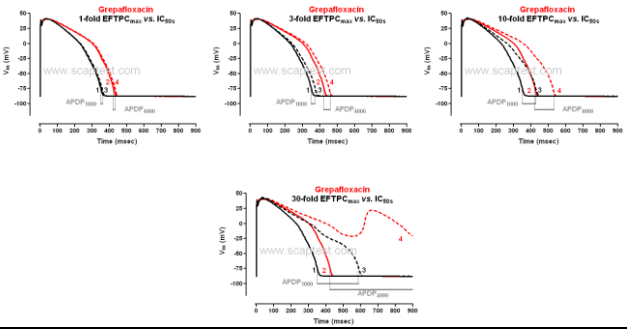


Transmural dispersion of repolarization

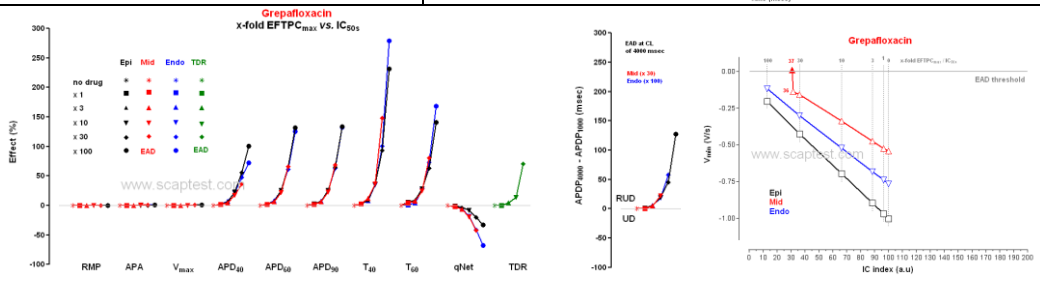


Reverse use dependence on midmyocardial myocytes

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



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3. Kramer J et al. (2013) *Sci.rep.* **3** : 2100
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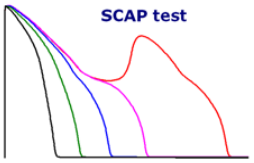

Drug

Imatinib

Tyrosine kinase inhibitor used to treat various leukemias, myelodysplastic/myeloproliferative disease, systemic mastocytosis, hypereosinophilic syndrome, dermatofibrosarcoma protuberans and gastrointestinal stromal tumors

Raw data

IC_{50s} (slope) (1)

I_{CaL} : ---- µM (---)
I_{Kr} : 19.51 µM (0.9)
I_{Na} : ---- µM (---)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$

0.18458 µM

De Alwis D et al. (2024)
www.hesiglobal.org/cctdatabase

TdP risk

Redfern (2) : not reported
Kramer (3) : not reported
CredibleMeds (4) : Possible risk of TdP (class 2)
CiPA (5) : not reported
WP (6) : 0/2 (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 = 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'

$$g_j = g_{control,j}\left[1+\left(\frac{D}{(IC50)_j}\right)^n\right]^{-1}$$

g = maximal conductance of channel 'j'
$G_{control}$= 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

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where
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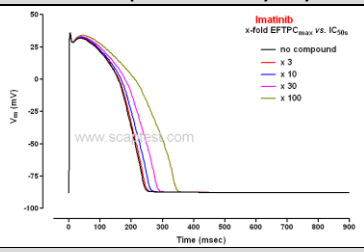
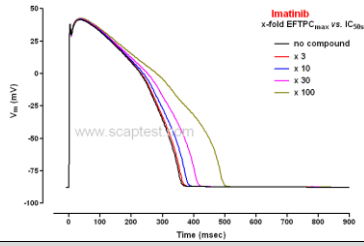
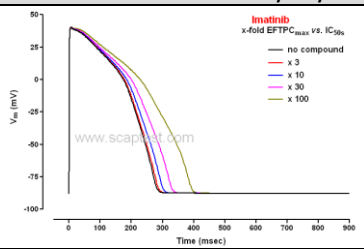
Human epicardial myocytes



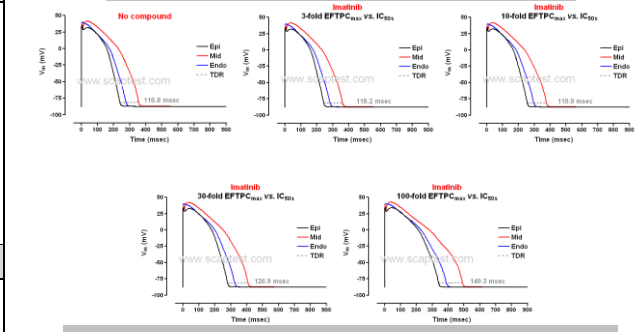
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarization



Reverse use dependence on midmyocardial myocytes

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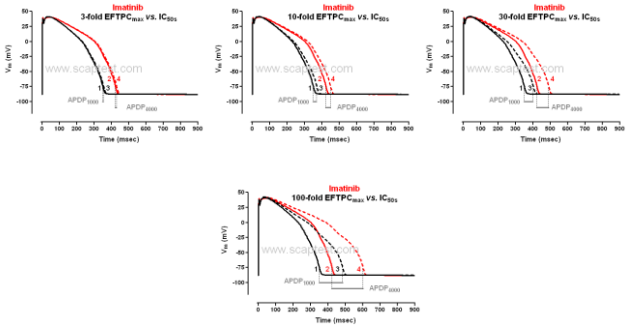
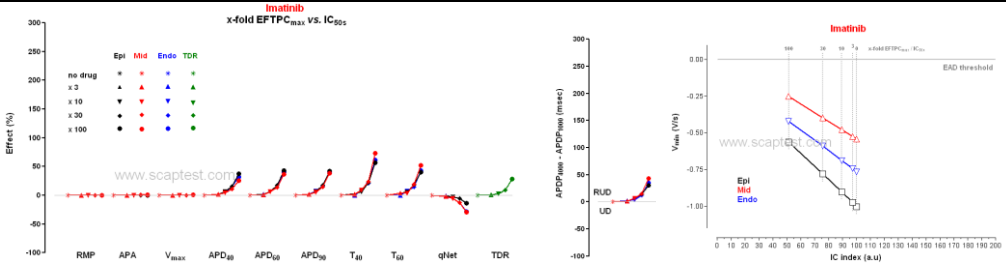


Summary



References

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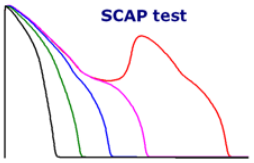

Drug

Irbesartan

Angiotensin AT_1 receptor antagonist used to treat hypertension, delay progression of diabetic nephropathy and congestive heart failure

Raw data

IC_{50s} (slope) [1]

I_{CaL} : ---- µM (---)
I_{Kr} : 193.0 µM (0.7)
I_{Na} : ---- µM (---)
I_{Ks} : 314.6 µM (1.1)
I_{to} : 7.2 µM (1.0)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ [1]

0.7 µM

TdP risk

Redfern [2] : not reported
Kramer [3] : not reported
CredibleMeds [4] : not classified with TdP risk (class 4)
CiPA [5] : not reported
WP [6] : not reported

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

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- 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}

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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'

$g_j = g_{control,j}\left[1+\left(\frac{D}{(IC50)_j}\right)^n\right]^{-1}$

g = maximal conductance of 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)
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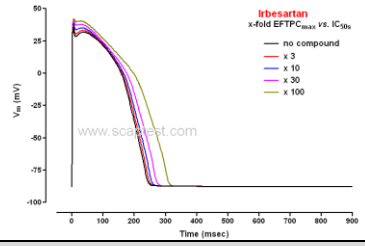
TDR and RUD estimation:
- TDR = APD_{90} mid - APD_{90} epi (at CL of 1000 msec)
- RUD = $APD_{90}P_{x000}$- $APD_{90}P_{1000}$

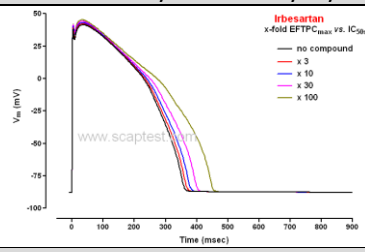
where
$APD_{90}P_x$ = APD_{90} with - APD_{90} without compound at CL x

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

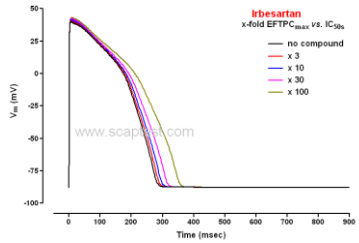
Human epicardial myocytes



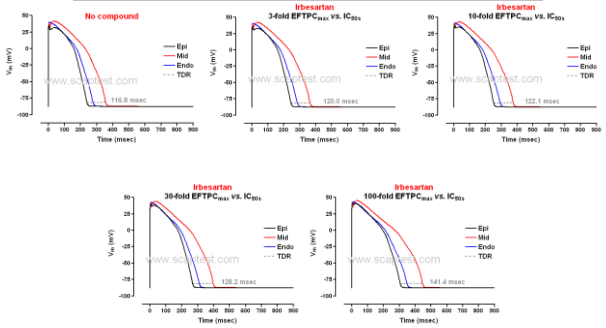
Human midmyocardial myocytes



Human endocardial myocytes

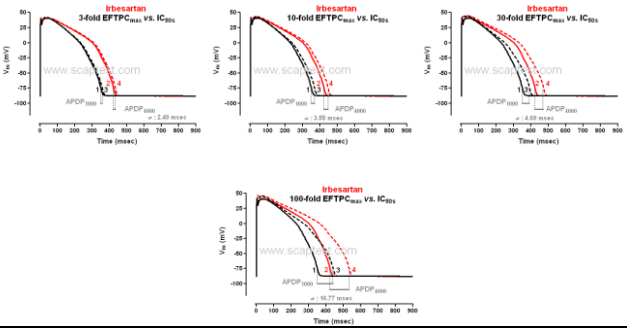


Transmural dispersion of repolarization

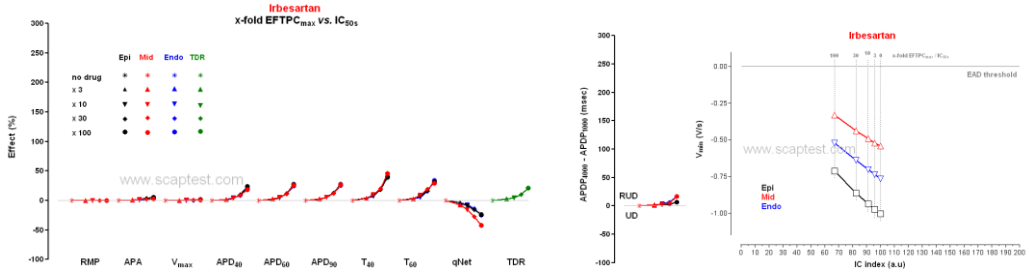


Reverse use dependence on midmyocardial myocytes

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



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2. Redfern WS et al. (2003) *Cardiovasc. Res.* **58 :** 32-45
3. Kramer J et al. (2013) *Sci.rep.* **3 :** 2100
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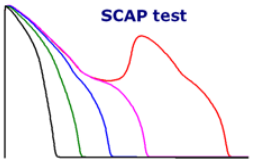
Abbreviations

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_{Kr}+I_{Na}+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, **V/s** : volt per second



Drug

Isradipine

Voltage-gated L-type Ca^{++} channel ($Ca_v1.2$) blocker used to treat hypertension

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 0.002 µM (1.0)
I_{to} : ---- µM (---)
I_{Kr} : 20.417 µM (1.0)
I_{NaL} : 7.762 µM (1.0)
I_{Na} : 21.38 µM (1.0)
I_{K1} : ---- µM (---)
I_{KS} : ---- µM (---)

$EFTPC_{max}$ [1]

0.0003 µM

TdP risk

Redfern [2] : not reported
Kramer [3] : not reported
CredibleMeds [4] : possible risk of TdP (Class 2)
CiPA [5] : not reported
WP [6] : 2/1 (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 = 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'

$g_j = g_{control\_j}\left[1+\left(\frac{D}{IC50j}\right)^{n}\right]^{-1}$

g = maximal conductance of 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

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- TDR = APD_{90} mid - APD_{90} epi (at CL of 1000 msec)
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IC index = (AFKr/((AFNaL+AFCaL)/2))*100
where
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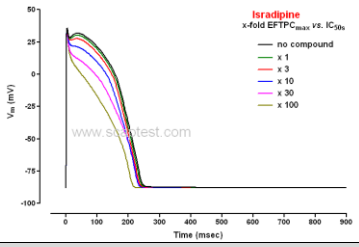
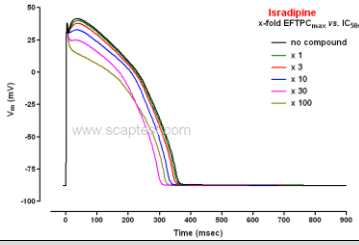
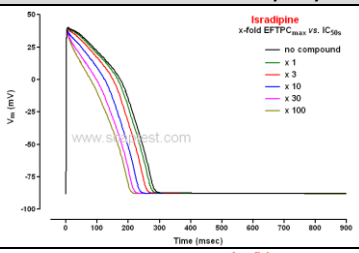
Human epicardial myocytes



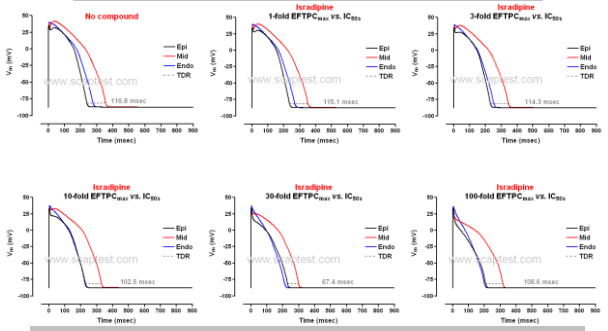
Human midmyocardial myocytes



Human endocardial myocytes

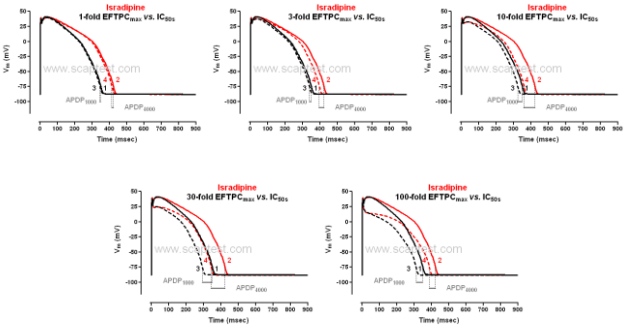


Transmural dispersion of repolarization

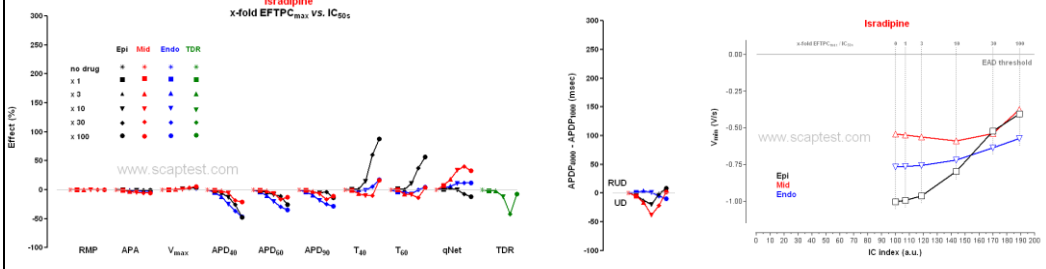


Reverse use dependence on midmyocardial myocytes

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



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Abbreviations

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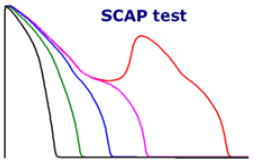

Drug

Loperamide

mu-opioid receptor agonist used to treat non specific or chronic diarrhea caused by inflammatory bowel disease or gastroenteritis
no longer marketed worldwide as syrup or drops (Onakpoya et al (2016) *BMC Med.* **14**: 10)

Raw data

IC_{50s} (slope) [1]

I_{CaL} : ---- µM (---)
I_{to} : ---- µM (---)
I_{Kr} : 0.0541 µM (1.0)
I_{NaL} : ---- µM (---)
I_{Na} : 0.239 µM (1.0)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$

0.0000650 µM

Eur. J. Clin. Pharmacol 2006,62:463-472

TdP risk

Redfern [2] : not reported
Kramer [3] : not reported
CredibleMeds [4] : conditional risk of TdP (class 3)
CiPA [5] : not reported
WP [6] : 1/1 (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'

$g_j = g_{control,j}\left[1+\left(\frac{D}{(IC50)_j}\right)^n\right]^{-1}$

g_j = maximal conductance of channel 'j'
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IC index = (AFKr/((AFNaL+AFCaL)/2))*100
where
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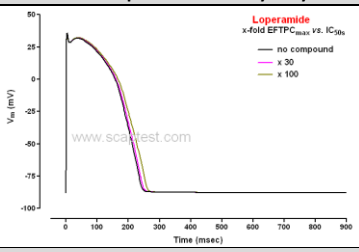
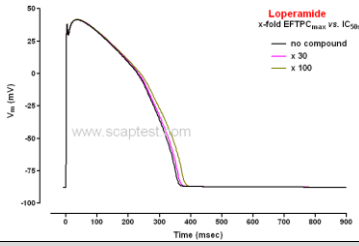
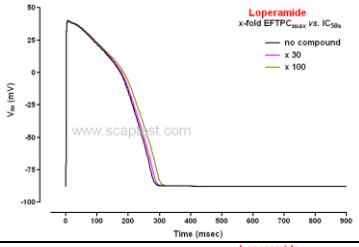
Human epicardial myocytes



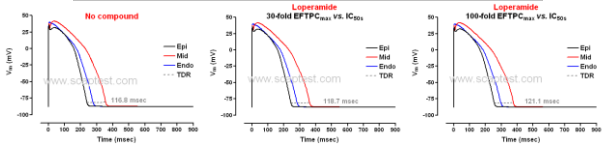
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarization



Reverse use dependence on midmyocardial myocytes

1 - CL 1000 msec without compound
2 - CL 4000 msec without compound
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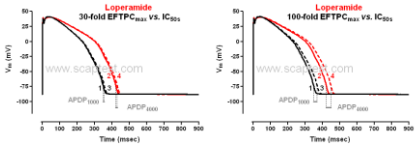
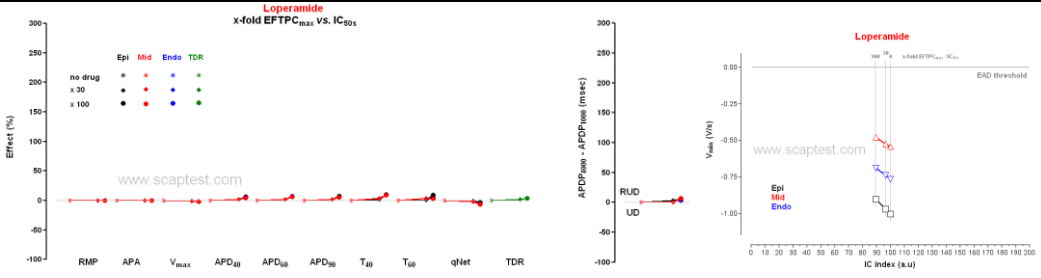


Summary



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3. Kramer J et al. (2013) *Sci.rep.* **3** : 2100
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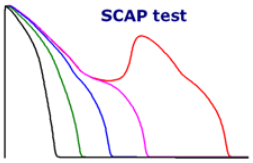

Drug

Manidipine

Voltage-gated L-type Ca^{++} channel ($Ca_v1.2$) blocker used to treat hypertension

Raw data

IC_{50s} (slope) [1]

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I_{to} : ---- µM (---)
I_{Kr} : 2.692 µM (1.0)
I_{NaL} : 10.715 µM (1.0)
I_{Na} : 8.511 µM (1.0)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ [1]

0.0001 µM

TdP risk

Redfern [2] : not reported
Kramer [3] : not reported
CredibleMeds [4] : not reported
CiPA [5] : not reported
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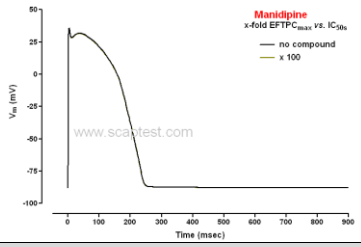
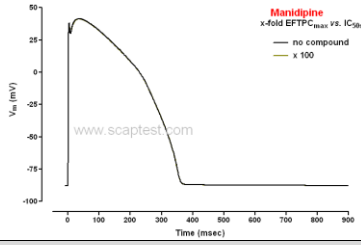
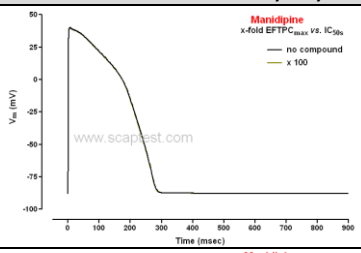


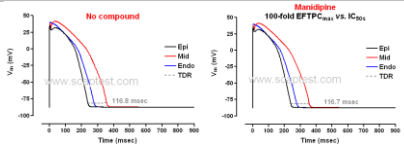
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarisation



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1 - CL 1000 msec without compound
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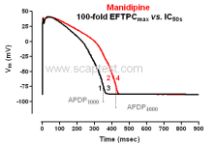
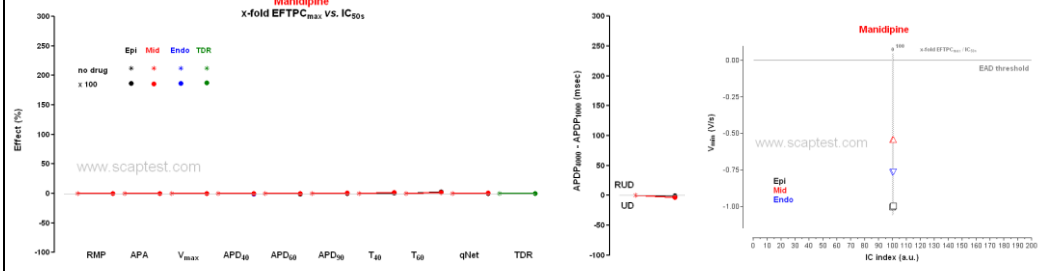


Summary



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5. CiPA (2016) www.ilsiextra.org/hesi/science/cardiac/cipa/Project
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7. O'Hara T et al. (2011) *PLoS Comput. Biol.* **7 :** e1002061_8
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Abbreviations

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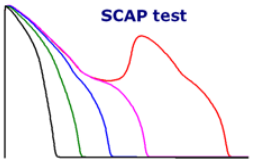


Drug

Maprotiline

Noradrenaline reuptake inhibitor, α_1- and α_2-adrenoceptor antagonist used as antidepressant to treat depressive illness, major depressive and bipolar disorders or anxiety

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 4.266 µM (1.0)
I_{to} : ---- µM (---)
I_{Kr} : 2.455 µM (1.0)
I_{NaL} : 2.042 µM (1.0)
I_{Na} : 1.148 µM (1.0)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ [1]

0.130 µM

TdP risk

Redfern [2] : numerous TdP reports (class 3)
Kramer [3] : not reported
CredibleMeds [4] : possible TdP risk (class 2)
CiPA [5] : not reported
WP [6] : 4/0 (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}

$I_j = g_j O (V - E_{ion})$; $g_j = g_{control\_j}\left[1+\left(\frac{D}{[IC50]_j}\right)^{n_j}\right]^{-1}$

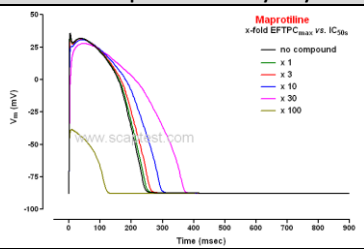
g = maximal conductance of channel 'j'; O=open probability of channel 'j'; V= voltage membrane; E_{ion}= reversal potential for species of ions which flows through channel 'j'; $g_{control\_j}$= drug-free maximal conductance of channel 'j'; IC50 = 50% of inhibition of a drug for channel 'j'; D= drug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

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

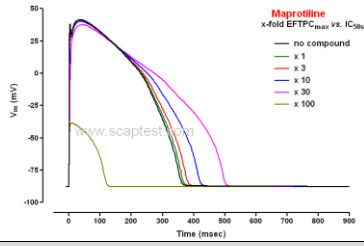
where
$APD_{90}P_x$ = APD_{90} with - APD_{90} without compound at CL x

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}

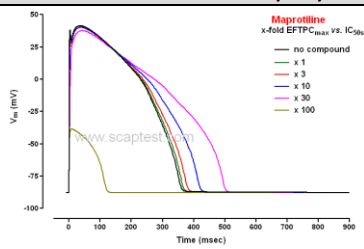
Human epicardial myocytes



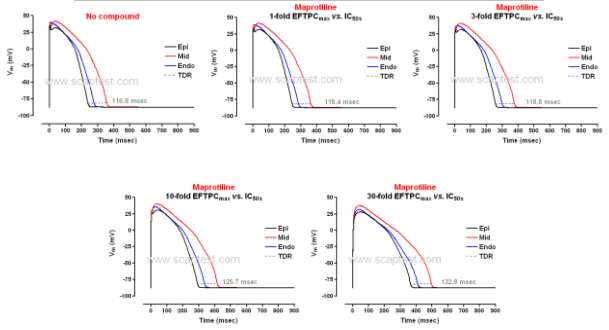
Human midmyocardial myocytes



Human endocardial myocytes

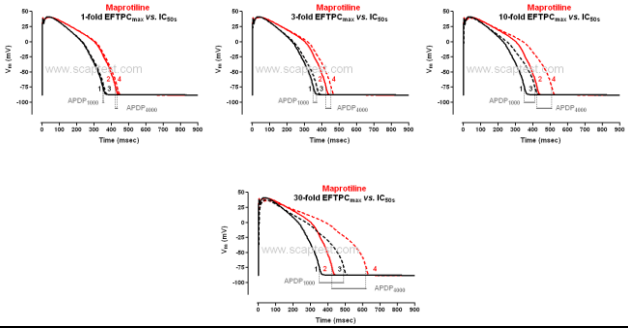


Transmural dispersion of repolarisation

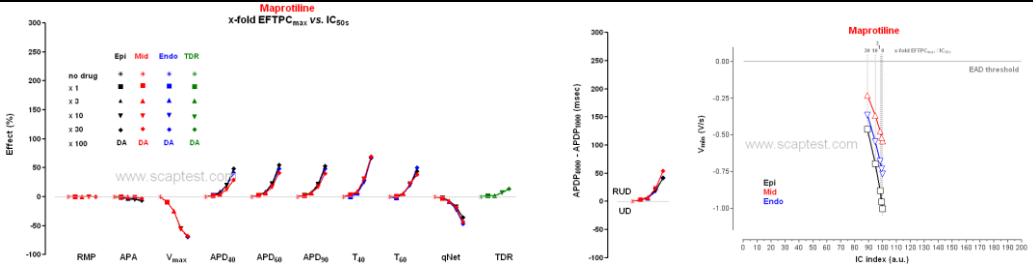


Reverse use dependence on midmyocardial myocytes

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



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2. Redfern WS et al. (2003) *Cardiovasc. Res.* **58 :** 32-45
3. Kramer J et al. (2013) *Sci.rep.* **3 :** 2100
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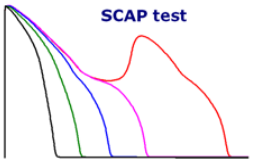

Drug

Mepivacaine

Voltage-gated Na^+ ($Na_v1.5$) channel blocker used for local or regional analgesia and anesthesia

Raw data

IC_{50s} (slope) [1]

I_{CaL} : ---- µM (---)
I_{to} : ---- µM (---)
I_{Kr} : 156.0 µM (0.89)
I_{NaL} : ---- µM (---)
I_{Na} : 81.4 µM (1.0)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$

12.7868 µM

De Alwis D et al. (2024)
www.hesiglobal.org/cctdatabase

TdP risk

Redfern [2] : not reported
Kramer [3] : not reported
CredibleMeds [4] : not reported
CiPA [5] : not reported
WP [6] : not reported

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'

$g_{j,drug} = g_{j,control} \left[1 + \left(\frac{D}{(IC50)_j}\right)^n\right]^{-1}$

$g_{j,drug}$ = drug-free maximal conductance of channel 'j'
IC50 = 50% of inhibition of a drug for channel 'j'
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n = hill slope

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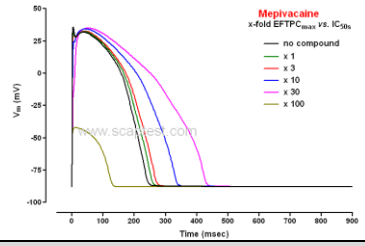
- TDR = APD_{90} mid - APD_{90} epi (at CL of 1000 msec)
- RUD = $APD_{90}P_{4000}$- $APD_{90}P_{1000}$

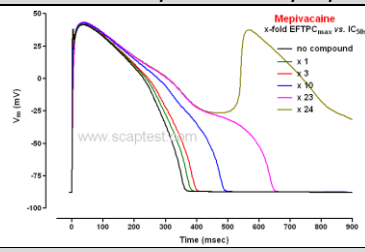
where
$APD_{90}P_x$ = APD_{90} with - APD_{90} without compound at CL x

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

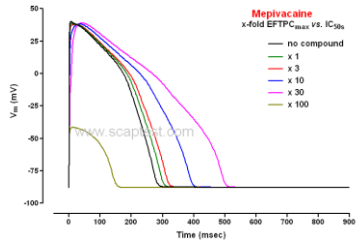
Human epicardial myocytes



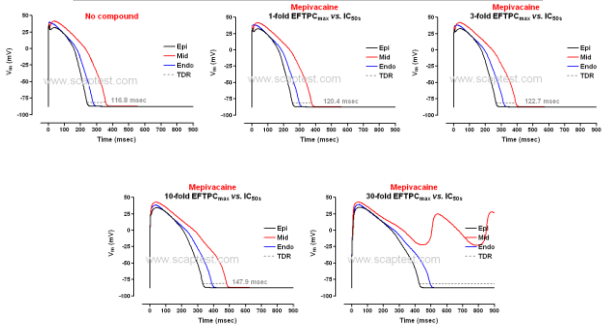
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarization



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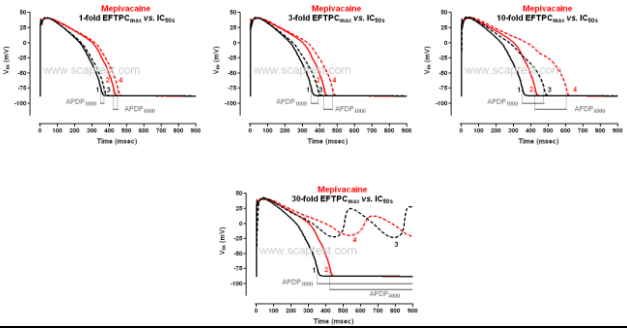

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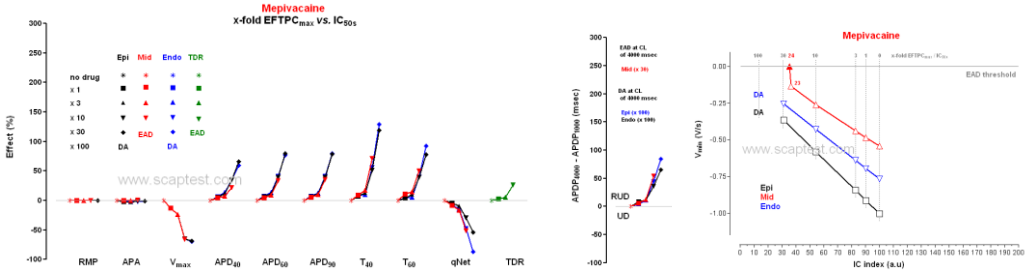

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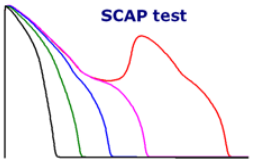

Drug

Mesoridazine

Dopamine D_2 and serotonin 5-HT_{2A} receptor antagonist used as antipsychotic to treat schizophrenia, organic brain disorders, alcoholism and psychoneuroses no longer marketed in USA [4]

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 16.218 µM (1.0)
I_{to} : ---- µM (---)
I_{Kr} : 0.347 µM (1.0)
I_{NaL} : 4.467 µM (1.0)
I_{Na} : 7.943 µM (1.0)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ [1]

2.483 µM

TdP risk

Redfern [2] : no published report of TdP (class 5)
Kramer [3] : not reported
CredibleMeds [4] : known TdP risk (class 1)
CiPA [5] : not reported
WP [6] : 3/1 (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

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- 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 = 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'

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

g = maximal conductance of channel 'j'
$G_{control}$= drug-free maximal conductance of channel 'j'
IC50 = 50% of inhibition of a drug for channel 'j'
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- TDR = APD_{90} mid - APD_{90} epi (at CL of 1000 msec)
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where
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where
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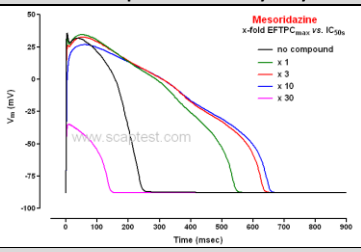
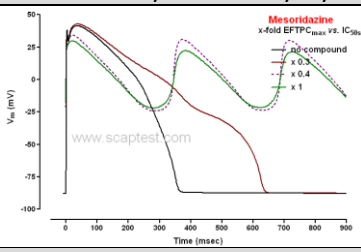
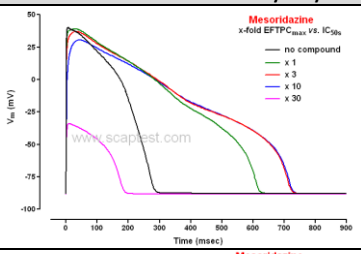
Human epicardial myocytes



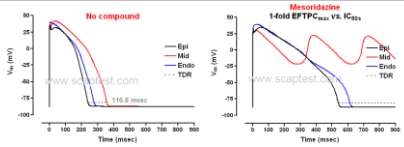
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarisation



Reverse use dependence on midmyocardial myocytes

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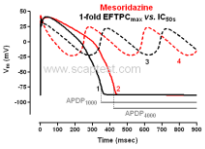
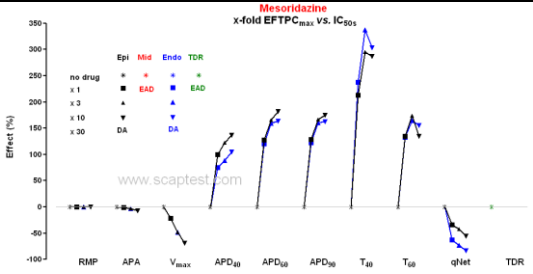
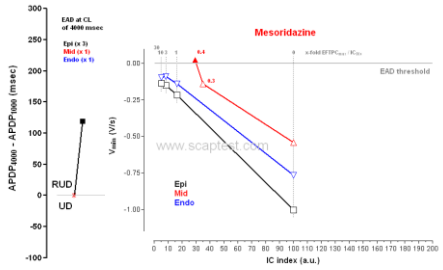


Summary





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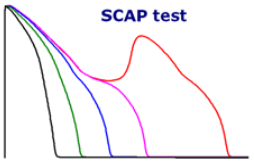


Drug

Metoclopramide

Dopamine D_2 antagonist used as antiemetic to treat gastroesophageal reflux disease, to prevent nausea and vomiting or to stimulate gastric emptying

Raw data

IC_{50s} (slope) (1)

I_{CaL} : ---- µM (---)
I_{Kr} : 5.4 µM (0.95)
I_{Na} : ---- µM (---)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ (1)

0.0957 µM

TdP risk

Redfern (2) : not reported
Kramer (3) : not reported
CredibleMeds (4) : conditional risk of TdP (class 3)
CiPA (5) : not reported
WP (6) : not reported

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 = 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')

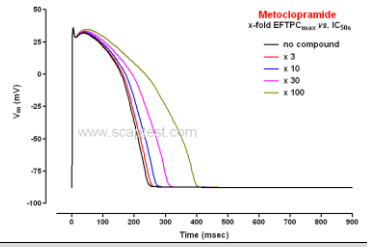
$g_j = g_{control\_j}\left[1+\left(\frac{D}{IC50_j}\right)^{n}\right]^{-1}$ (g = maximal conductance of channel 'j', $g_{control\_j}$= drug-free maximal conductance of channel 'j', IC50 = 50% of inhibition of a drug for channel 'j', D= drug concentration (EFTPC for example), n = hill slope)

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

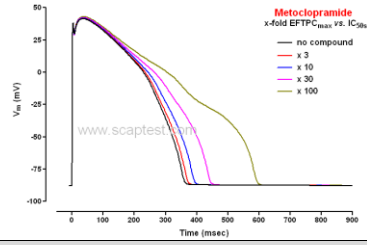
where
$APD_{90}P_x$ = APD_{90} with - APD_{90} without compound at CL x

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}

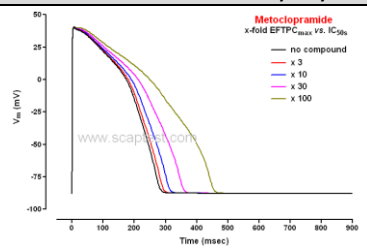
Human epicardial myocytes



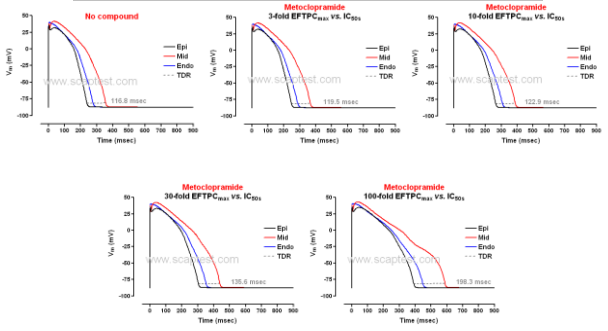
Human midmyocardial myocytes



Human endocardial myocytes

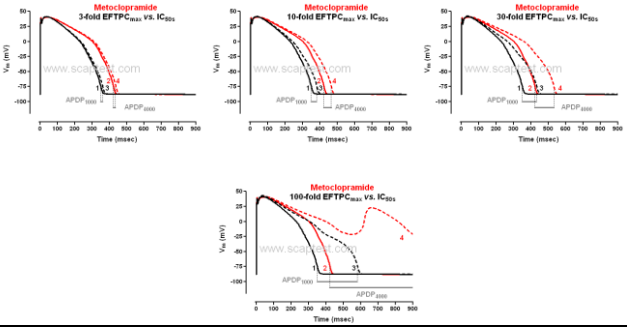


Transmural dispersion of repolarisation

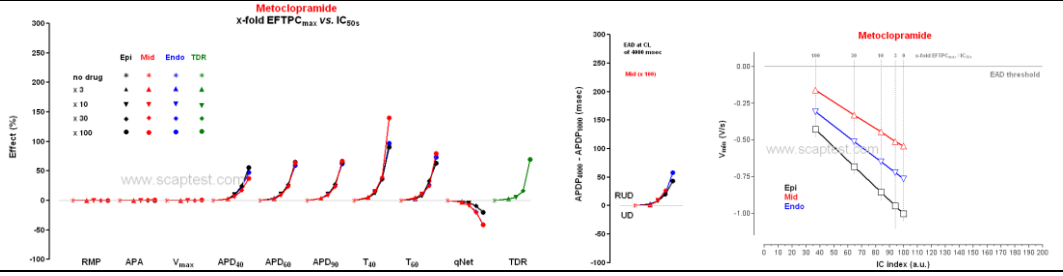


Reverse use dependence on midmyocardial myocytes

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



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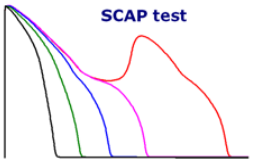
2. Redfern WS et al. (2003) *Cardiovasc. Res.* **58**: 32-45
3. Kramer J et al. (2013) *Sci.rep.* **3** : 2100
4. Woosley RL (2015) www.CredibleMeds.org
5. CiPA (2016) www.ilsiextra.org/hesi/science/cardiac/cipa/Project
6. Wisnioswska B et al. (2017) *Drug discovery today* **22 :** 10-16
7. O'Hara T 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, **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_{Kr}+I_{Ks}+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, **V/s** : volt per second



Drug

Mizolastine

Histamine H_1 receptor antagonist used to treat chronic allergic rhinitis and chronic idiopathic urticaria

Raw data

IC_{50s} (slope) [1]

I_{CaL} : ---- µM (---)
I_{Kr} : 0.35 µM (1.0)
I_{Na} : ---- µM (---)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ [1]

0.0087 µM

TdP risk

Redfern [2] : no published report of TdP (class 5)
Kramer [3] : not reported
CredibleMeds [4] : not classified with TdP risk (class 4)
CiPA [5] : not reported
WP [6] : 2/1 (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 = 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'

$g_j = g_{control\_j}\left[1+\left(\frac{D}{IC50_j}\right)^{n_j}\right]^{-1}$ g = maximal conductance of 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

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- TDR = APD_{90} mid - APD_{90} epi (at CL of 1000 msec)
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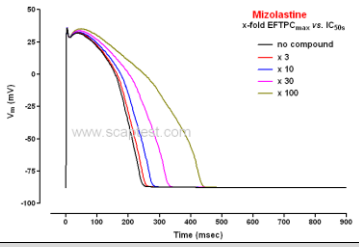
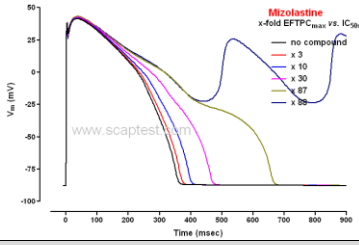
where
$APD_{90}P_x$ = APD_{90} with - APD_{90} without compound at CL x

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}

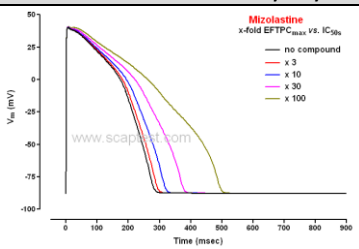
Human epicardial myocytes



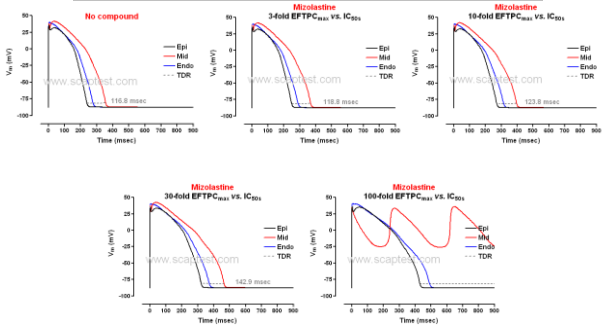
Human midmyocardial myocytes



Human endocardial myocytes

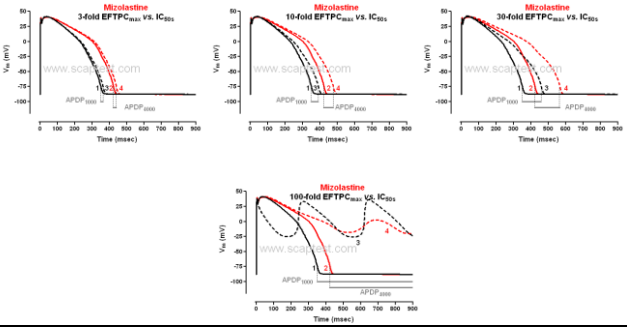


Transmural dispersion of repolarization

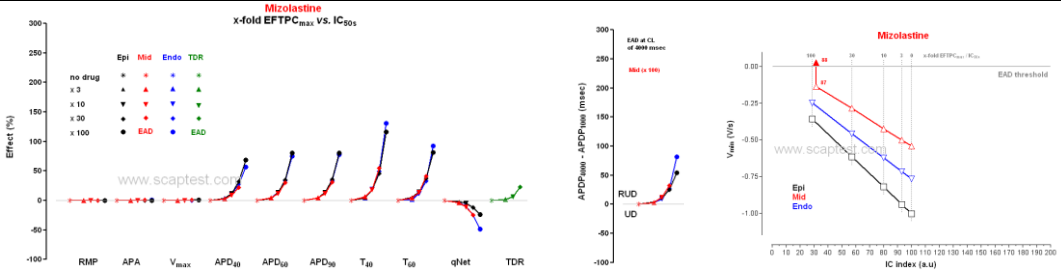


Reverse use dependence on midmyocardial myocytes

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



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4. Woosley RL (2015) www.CredibleMeds.org
5. CiPA (2016) www.ilsiextra.org/hesi/science/cardiac/cipa/Project
6. Wiśniowska B et al. (2017) *Drug discovery today* **22 :** 10-16
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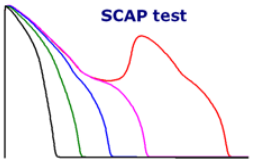
8. Mirams GR et al. (2011) *Cardiovasc. Res.* **91 :** 53-61
9. Christophe B & Crumb WJ Jr (2019) *J Pharmacol Toxicol Methods* **96 :** 15-26

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_{Kr}+I_{Ks}+I_{to}+I_{NaL}+I_{K1}, **RMP** : resting membrane potential, **RUD** : reverse use dependence, $T_{40,60}$: APD_{60}-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



Drug

Nifekalant

Potassium voltage-gated cardiac channel (K_v11.1) blocker under evaluation (clinical trial NCT03855826) as class III antiarrhythmic to treat cardiac arrhythmia

Raw data

IC_{50s} (slope) [1]

I_{CaL} : ---- µM (---)
I_{to} : ---- µM (---)
I_{Kr} : 7.9 µM (1.0)
I_{NaL} : ---- µM (---)
I_{Na} : ---- µM (---)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$

0.6517 µM*

*Zhang M et al (2013) *J. Chromotogr. B Analyt. Technol. Biomed. Life Sci.* **938** : 105-110

TdP risk

Redfern [2] : not reported
Kramer [3] : not reported
CredibleMeds [4] : known TdP risk (class 1)
CiPA [5] : not reported
WP [6] : not reported

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 = 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')

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- 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
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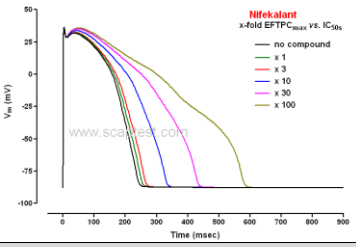
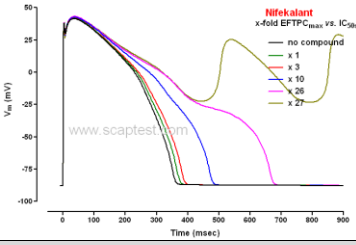
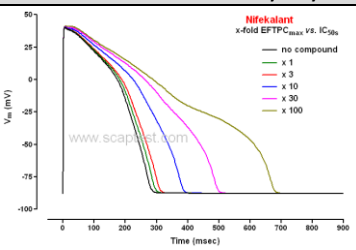
Human epicardial myocytes



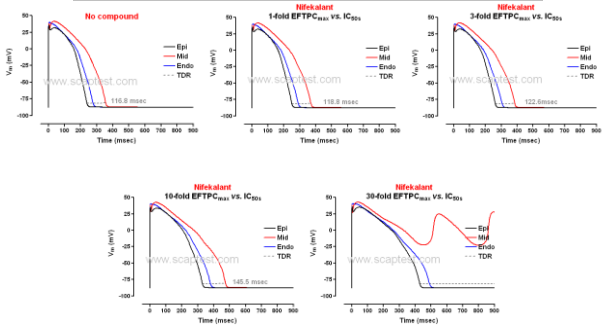
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarization



Reverse use dependence on midmyocardial myocytes

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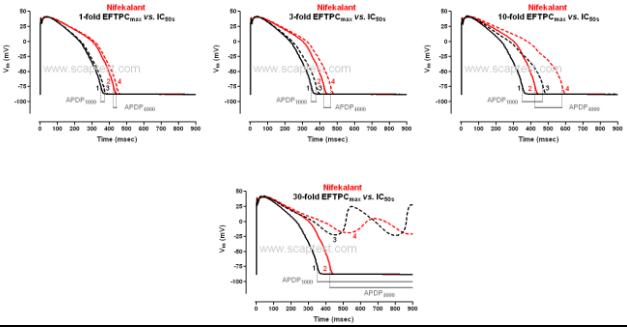
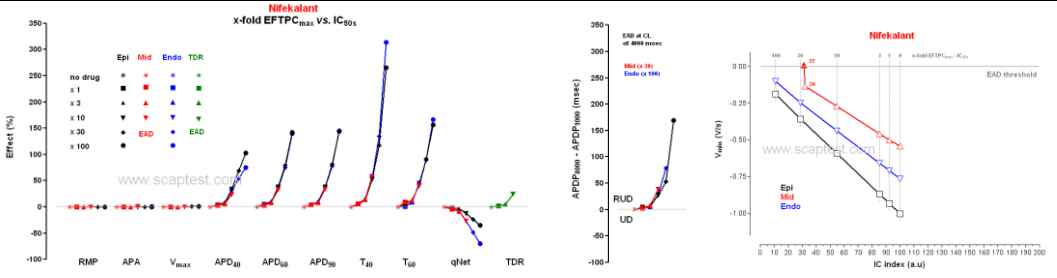
4 - CL 4000 msec with compound



Summary



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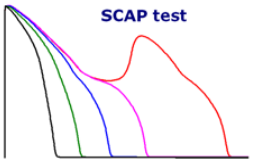

Drug

Nilvadipine

Voltage-gated L-type Ca^{++} channel ($Ca_v1.2$) blocker used to treat arterial hypertension

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 0.004 µM (1.0)
I_{to} : ---- µM (---)
I_{Kr} : 19.953 µM (1.0)
I_{NaL} : 2.291 µM (1.0)
I_{Na} : 0.955 µM (1.0)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ [1]

0.0005 µM

TdP risk

Redfern [2] : not reported
Kramer [3] : not reported
CredibleMeds [4] : not reported
CiPA [5] : not reported
WP [6] : not reported

Results

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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
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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}

$I_j = g_j O (V - E_{ion})$; $g_j = g_{j\,control\,j}\left[1+\left(\frac{D}{(IC50)_j}\right)^n\right]^{-1}$

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'
$g_{j\,control\,j}$= drug-free maximal conductance of channel 'j'
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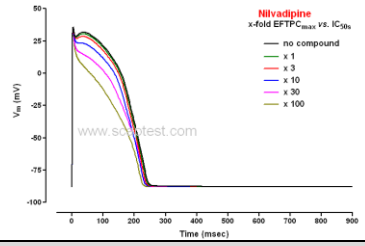
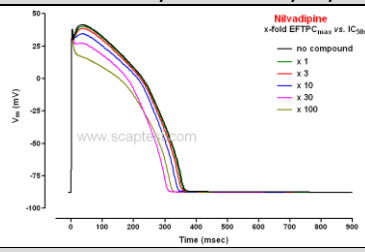
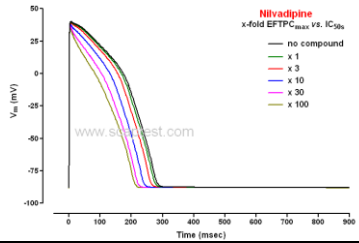
Human epicardial myocytes



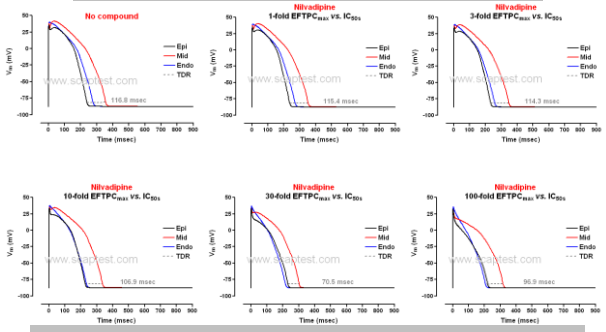
Human midmyocardial myocytes



Human endocardial myocytes

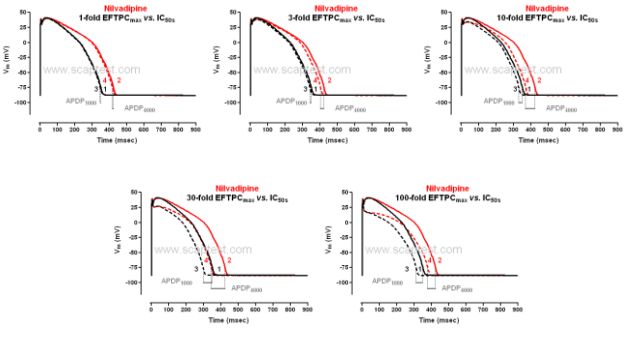


Transmural dispersion of repolarisation

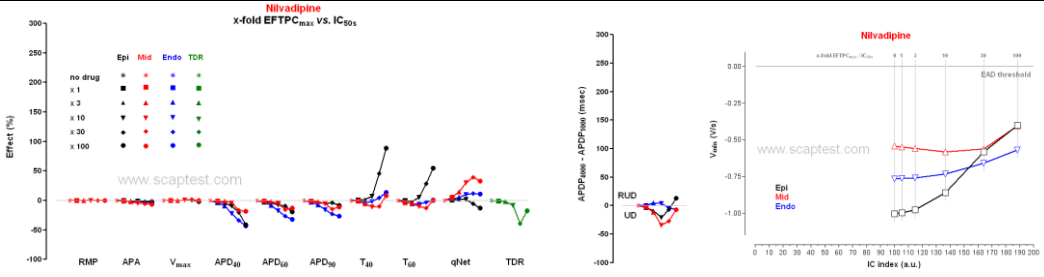


Reverse use dependence on midmyocardial myocytes

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



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3. Kramer J et al. (2013) *Sci.rep.* **3** : 2100
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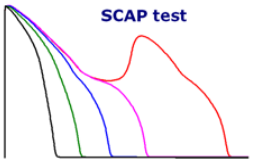
8. Mirams GR et al. (2011) *Cardiovasc. Res.* **91** : 53-61
9. Christophe B & Crumb WJ Jr (2019) *J Pharmacol Toxicol Methods* **96** : 15-26

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_{to}+I_{NaL}+I_{K1}, **RMP** : resting membrane potential, **RUD** : reverse use dependence, **$T_{40,60}$** : APD_{90}-APD_{40} or APD_{90} (°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



Drug

Nortriptyline

Noradrenaline and serotonin reuptake inhibitor used as antidepressant to treat depression

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 3.467 µM (1.0)
I_{to} : ---- µM (---)
I_{Kr} : 3.020 µM (1.0)
I_{NaL} : 2.692 µM (1.0)
I_{Na} : 0.871 µM (1.0)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ [1]

0.053 µM

TdP risk

Redfern [2] : not reported
Kramer [3] : not reported
CredibleMeds [4] : possible risk of TdP (class 2)
CiPA [5] : not reported
WP [6] : 2/1 (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'

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

$g_{control,j}$ = maximal conductance of channel 'j'
$g_{drug,j}$ = 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:

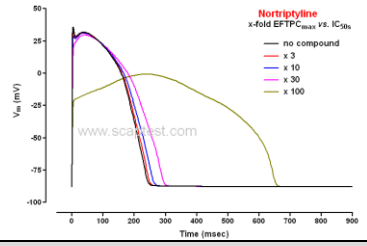
- TDR = APD_{90} mid - APD_{90} epi (at CL of 1000 msec)
- RUD = $APD_{90}P_{4000}$- $APD_{90}P_{1000}$

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

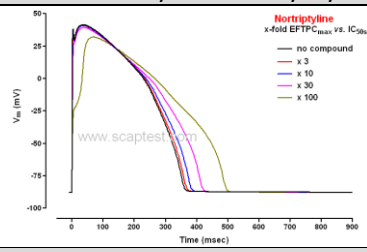
IC index calculation [9]:

IC index = (AFKr/((AFNaL+AFCaL)/2))*100
where
AFKr, AFNaL and AFCaL = active fraction (%) of the I_{Ks}, I_{NaL} and I_{CaL}.

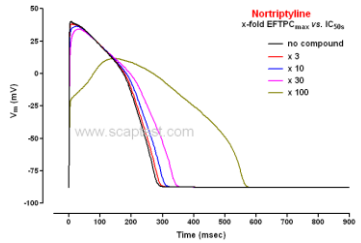
Human epicardial myocytes



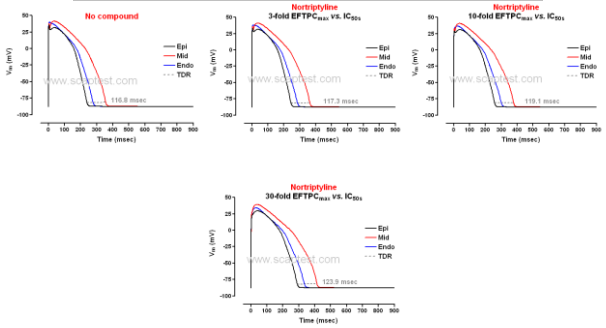
Human midmyocardial myocytes



Human endocardial myocytes

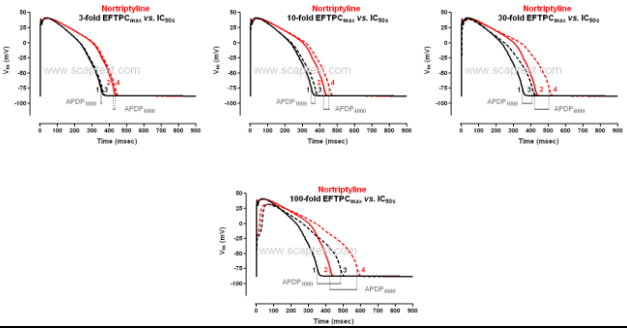


Transmural dispersion of repolarization

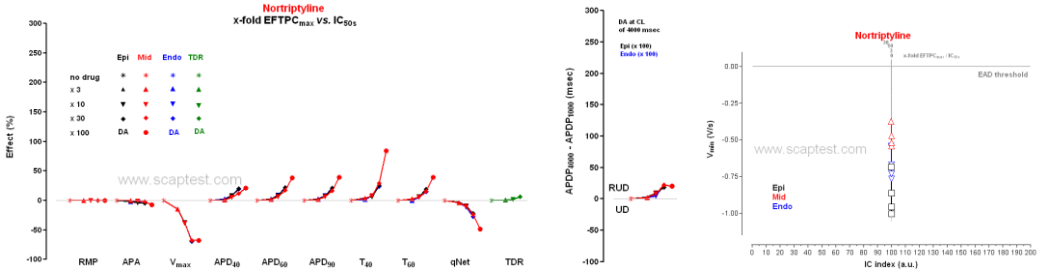


Reverse use dependence on midmyocardial myocytes

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



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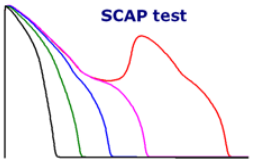

Drug

Oseltamivir

Neuraminidase inhibitor used to treat influenza

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 4263 µM (1.0)
I_{Kr} : 231 µM (1.0)
I_{Na} : 3545 µM (1.0)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ *

0.12067 µM

* www.go.drugbank.com

TdP risk

Redfern [2] : not reported
Kramer [3] : not reported
CredibleMeds [4] : not classified with TdP risk (class 4)
CiPA [5] : not reported
WP [6] : not reported

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

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- 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}

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g = maximal conductance of channel 'j'
O=open probability of channel 'j'
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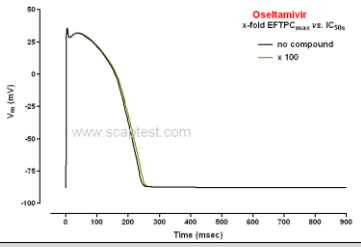
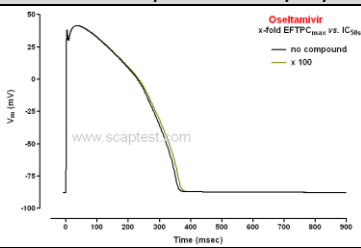
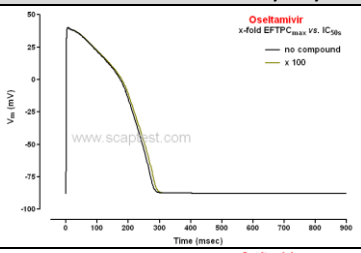
Human epicardial myocytes



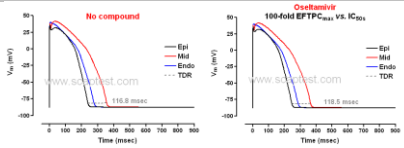
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarization



Reverse use dependence on midmyocardial myocytes

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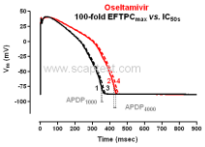
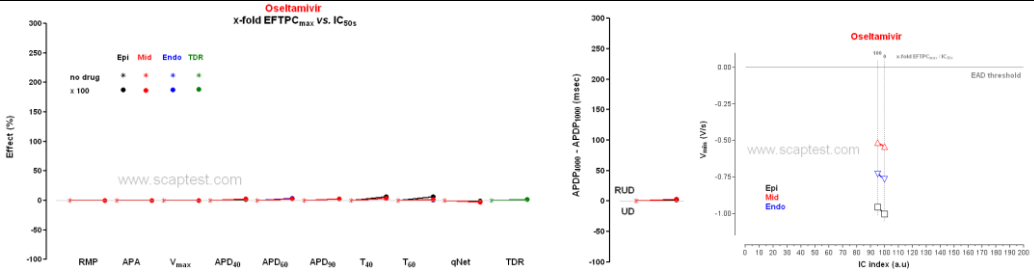
4 - CL 4000 msec with compound



Summary



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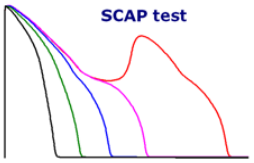

Drug

Pitolisant

Histamine H_3 antagonist and inverse agonist used to treat narcolepsy in adult

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 9.5 µM (1.0)
I_{to} : 11.4 µM 1.0)
I_{Kr} : 1.3 µM (1.0)
I_{NaL} : ---- µM (---)
I_{Na} : 26.4 µM (1.0)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ *

0.1604 µM

*www.go.drugbank.com

TdP risk

Redfern [2] : not reported
Kramer [3] : not reported
CredibleMeds [4] : possible risk of TdP (Class 2)
CiPA [5] : not reported
WP [6] : not reported

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 = 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'

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- RUD = $APD_{90}P_{x000}$- $APD_{90}P_{1000}$

where
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IC index = (AFKr/((AFNaL+AFCaL)/2))*100
where
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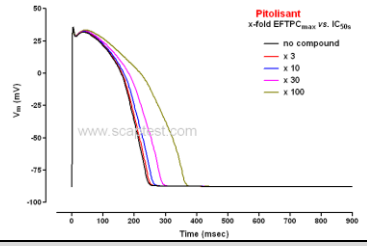
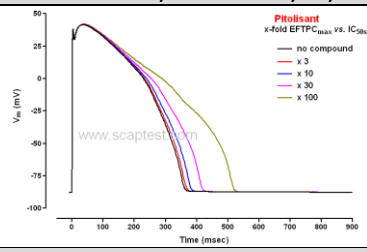
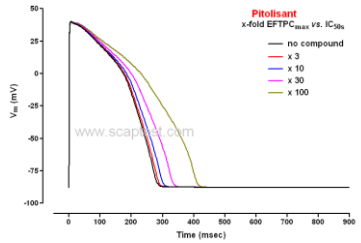
Human epicardial myocytes



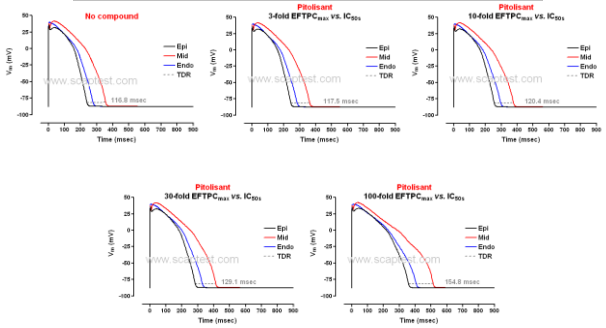
Human midmyocardial myocytes



Human endocardial myocytes

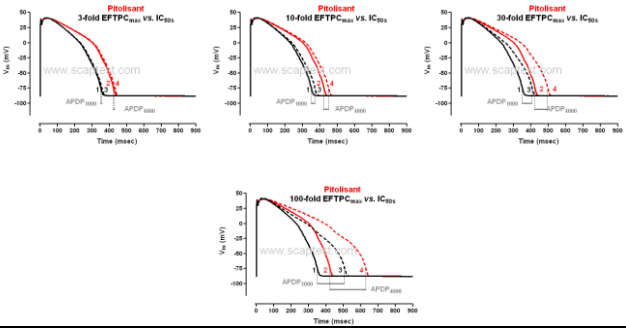


Transmural dispersion of repolarisation



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



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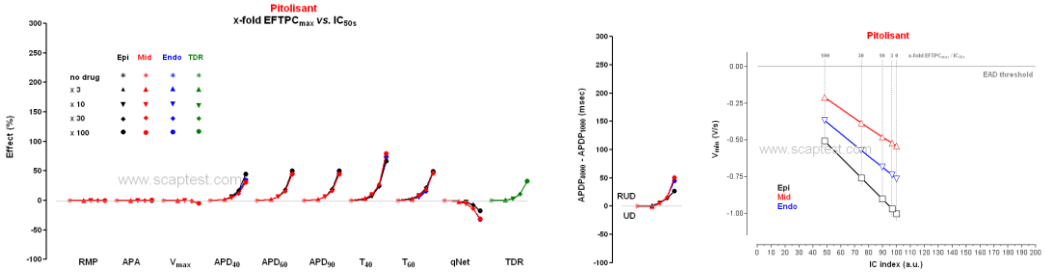

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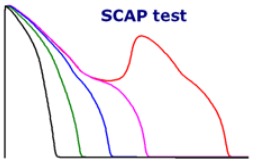

Drug

Procaine

Voltage-gated Na^+ ($Na_v1.5$) channel blocker used as local anaesthetic to manage anaesthesia, peripheral or spinal nerve block

Raw data

IC_{50s} (slope) [1]

I_{CaL} : ---- µM (---)
I_{to} : ---- µM (---)
I_{Kr} : 23.442 µM (1.0)
I_{NaL} : 151.356 µM (1.0)
I_{Na} : 128.825 µM (1.0)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ [1]

9.945 µM

TdP risk

Redfern [2] : not reported
Kramer [3] : not reported
CredibleMeds [4] : not reported
CiPA [5] : not reported
WP [6] : not reported

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
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- 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}

$I_j = g_j O (V - E_{ion})$; $g_j = g_{j\,control,j}\left[1+\left(\frac{D}{(IC50)_j}\right)^n\right]^{-1}$

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

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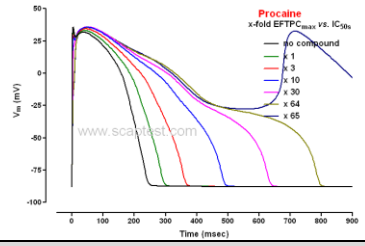
- TDR = APD_{90} mid - APD_{90} epi (at CL of 1000 msec)
- RUD = $APD_{90}P_{4000}$- $APD_{90}P_{1000}$

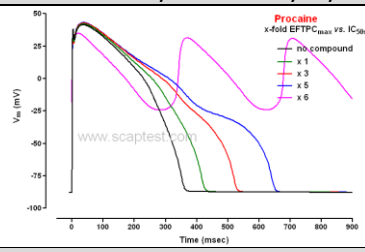
where
$APD_{90}P_x$ = APD_{90} with - APD_{90} without compound at CL x

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

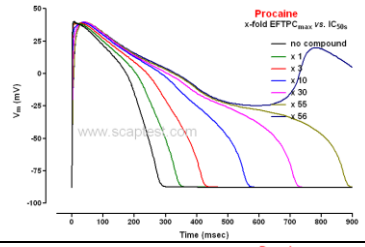
Human epicardial myocytes



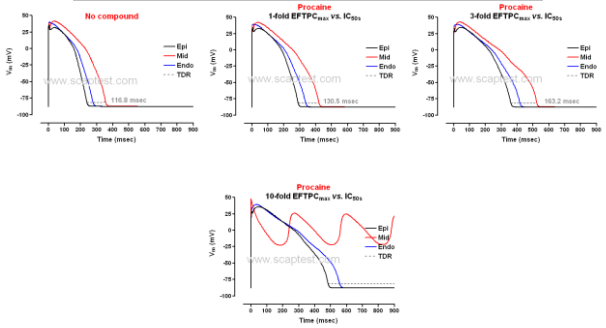
Human midmyocardial myocytes



Human endocardial myocytes

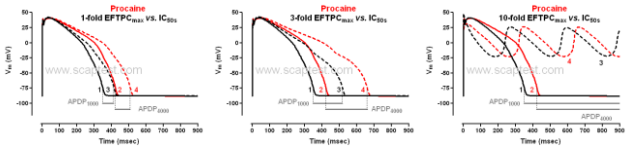


Transmural dispersion of repolarisation

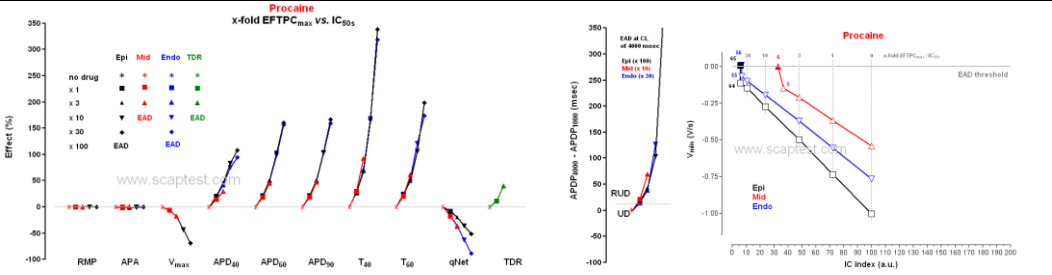


Reverse use dependence on midmyocardial myocytes

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



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1. Watt ED et al. (2022) *J.Pharmacol.Tox.Methods* **118** : 107213
2. Redfern WS et al. (2003) *Cardiovasc. Res.* **58** : 32-45
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8. Mirams GR et al. (2011) *Cardiovasc. Res.* **91** : 53-61
9. Christophe B & Crumb WJ Jr (2019) *J Pharmacol Toxicol Methods* **96** : 15-26

Abbreviations

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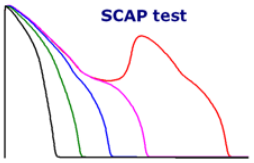

Drug	**Promethazine** H_1 receptor antagonist used to treat allergic conditions, nausea, vomiting and motion sickness

Raw data

IC_{50s} (slope) [1]	$EFTPC_{max}$ [1]	TdP risk
I_{CaL} : ---- µM (---) I_{Kr} : 1.46 µM (1.07) I_{Na} : ---- µM (---) I_{Ks} : ---- µM (---) I_{to} : ---- µM (---) I_{NaL} : ---- µM (---) I_{K1} : ---- µM (---)	0.00541 µM	Redfern [2] : not reported Kramer [3] : not reported CredibleMeds [4] : possible risk of TdP (Class 2) CiPA [5] : not reported WP [6] : 2/1 (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):
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IC index = (AFKr/((AFNaL+AFCaL)/2))*100
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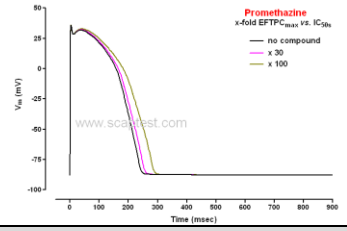
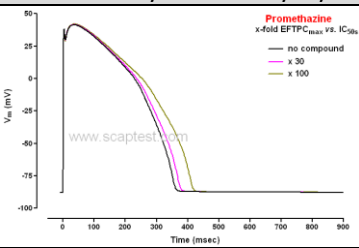
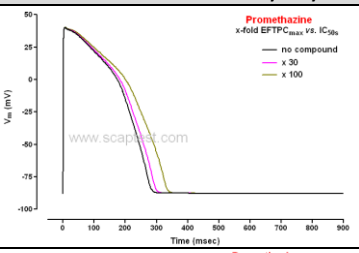
Human epicardial myocytes



Human midmyocardial myocytes



Human endocardial myocytes



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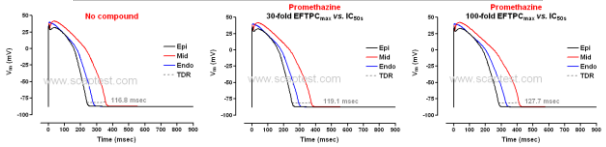

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1 - CL 1000 msec without compound
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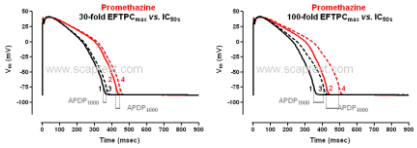
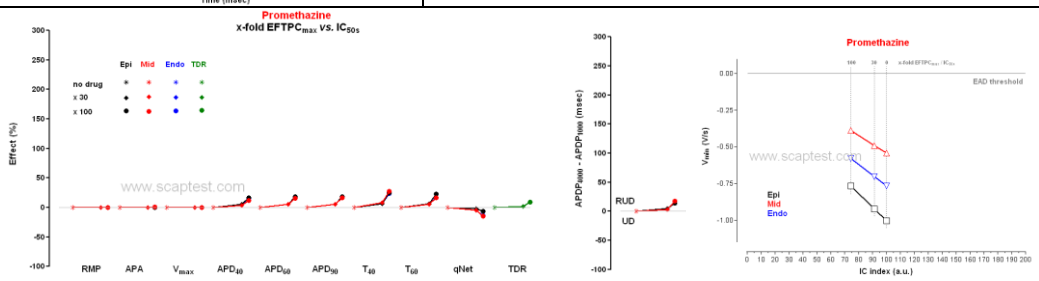


Summary



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2. Redfern WS et al. (2003) *Cardiovasc. Res.* **58**: 32-45
3. Kramer J et al. (2013) *Sci.rep.* **3** : 2100
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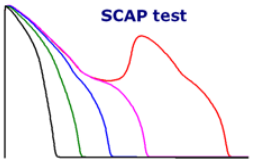

Drug

Ribociclib

Cycline-dependent kinase 4 and 6 (CDK4/6) inhibitor used to treat HR+, HER2- advanced or metastatic breast cancer

Raw data

IC_{50s} (slope) (1)

I_{CaL} : ---- µM (---)
I_{to} : ---- µM (---)
I_{Kr} : 8.511 µM (1.0)
I_{NaL} : ---- µM (---)
I_{Na} : 66.069 µM (1.0)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ (1)

0.547 µM

TdP risk

Redfern (2) : not reported
Kramer (3) : not reported
CredibleMeds (4) : possible risk of TdP (class 2)
CiPA (5) : not reported
WP (6) : not reported

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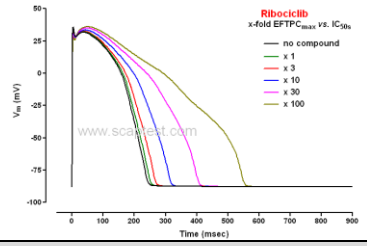
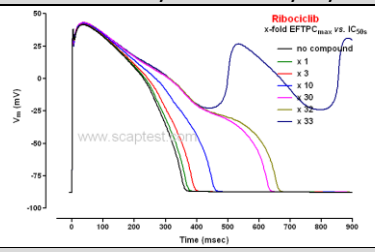
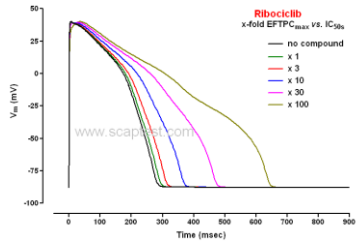


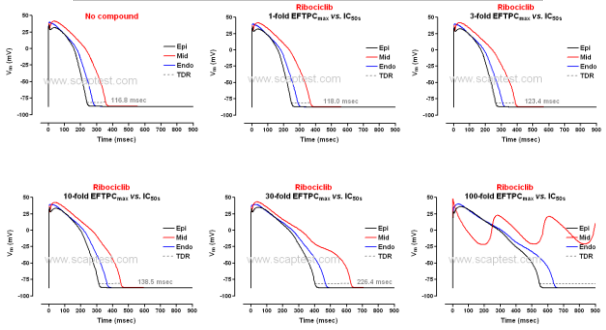
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarisation



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2 - CL 4000 msec without compound
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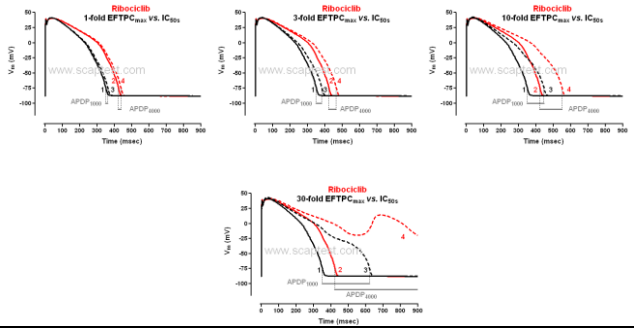

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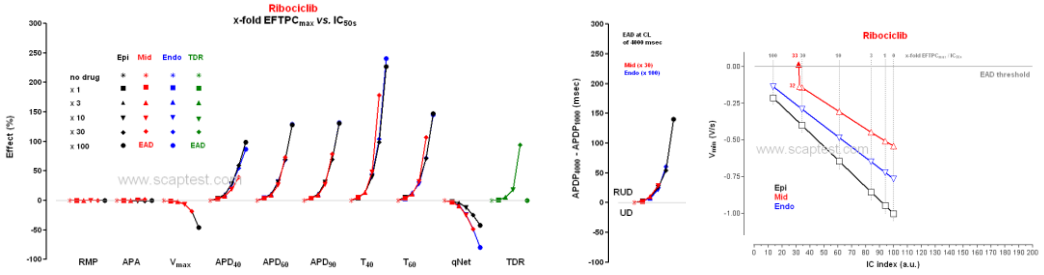

References

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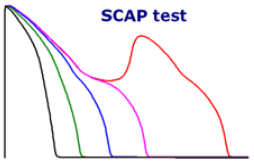

Drug

Ropivacaine

Voltage-gated Na^+ ($Na_v1.5$) channel blocker used for local or regional anesthesia during surgery and for short-term management of acute pain

Raw data

IC_{50s} (slope) [1]

I_{CaL} : ---- µM (---)
I_{to} : ---- µM (---)
I_{Kr} : 15.488 µM (1.0)
I_{NaL} : 10.000 µM (1.0)
I_{Na} : 12.882 µM (1.0)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ [1]

0.612 µM

TdP risk

Redfern [2] : not reported
Kramer [3] : not reported
CredibleMeds [4] : not reported
CiPA [5] : not reported
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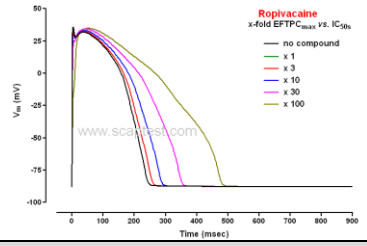
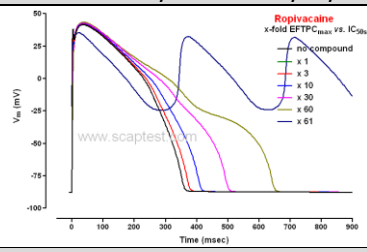
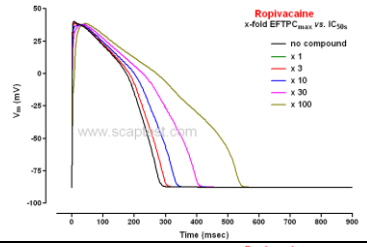


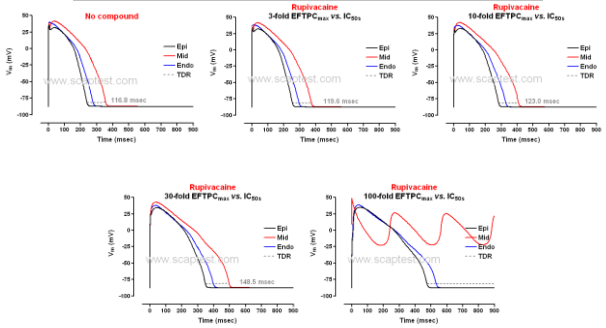
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarisation



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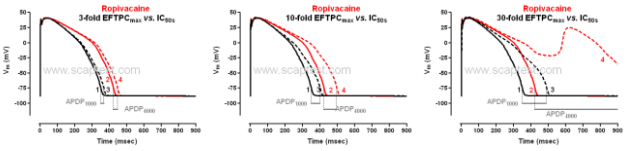
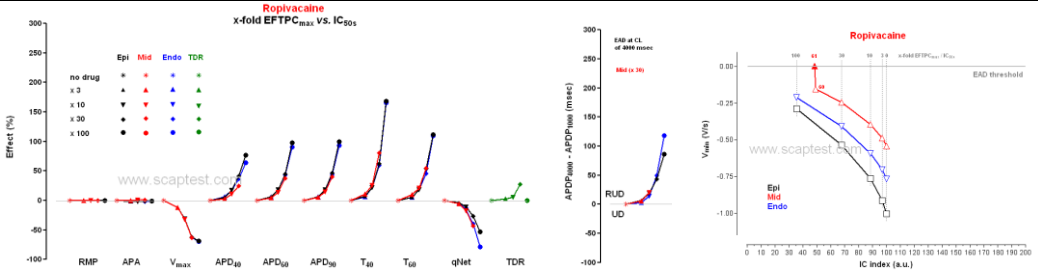
3 - CL 1000 msec with compound
4 - CL 4000 msec with compound



Summary



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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
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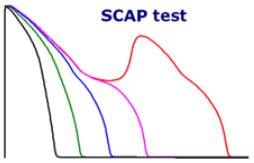
7. O'Hara T et al. (2011) *PLoS Comput. Biol.* **7** : e1002061_8
8. Mirams GR et al. (2011) *Cardiovasc. Res.* **91** : 53-61
9. Christophe B & Crumb WJ Jr (2019) *J Pharmacol Toxicol Methods* **96** : 15-26

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 $I_{CaL}+I_{to}+I_{Na}+I_{to}+I_{NaL}+I_{Kr}$, **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



Drug

Rilpivirine

Non-nucleoside reverse transcriptase inhibitor used to treat human immunodeficiency virus type 1 (HIV)

Raw data

IC_{50s} (slope) [1]

I_{CaL} : ---- µM (---)
I_{to} : ---- µM (---)
I_{Kr} : 0.687 µM (1.0)
I_{NaL} : ---- µM (---)
I_{Na} : ---- µM (---)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ [1]

0.006741 µM

TdP risk

Redfern [2] : not reported
Kramer [3] : not reported
CredibleMeds [4] : possible risk of TdP (Class 2)
CiPA [5] : not reported
WP [6] : 0/1 (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'

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

g_j = maximal conductance of 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:

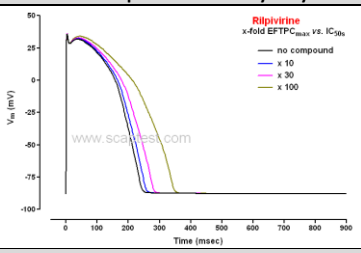
- TDR = APD_{90} mid - APD_{90} epi (at CL of 1000 msec)
- RUD = $APD_{90}P_{4000}$-$APD_{90}P_{1000}$

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

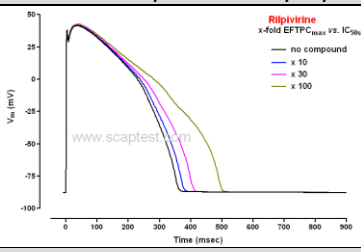
IC index calculation [9]:

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

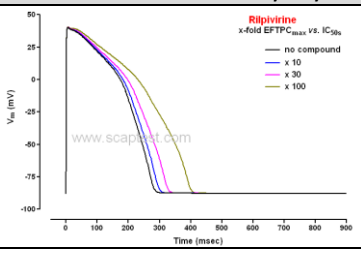
Human epicardial myocytes



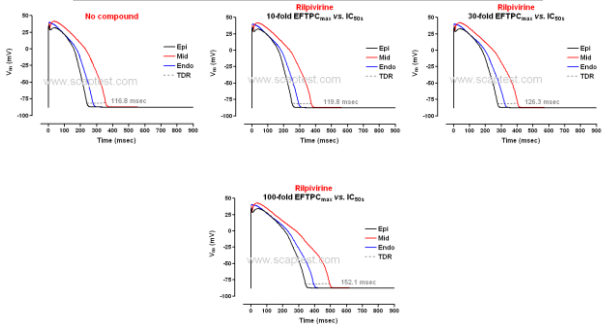
Human midmyocardial myocytes



Human endocardial myocytes

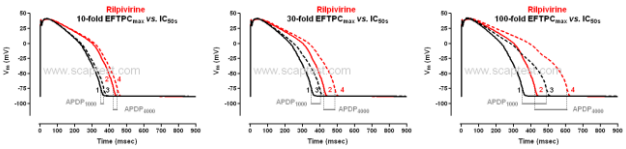


Transmural dispersion of repolarisation

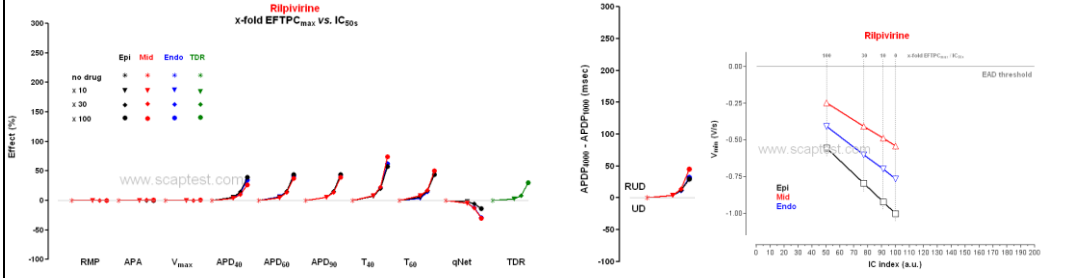


Reverse use dependence on midmyocardial myocytes

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



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6. Wisnioswska B et al. (2017) *Drug discovery today* **22 :** 10-16
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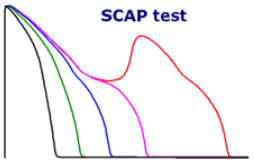
9. Christophe B et al. (2019) *J Pharmacol Toxicol Methods* **96 :** 15-26

Abbreviations

AP : action potential, **APA** : AP amplitude, **$APD_{40, 60 or 90}$** : AP duration at 40, 60 or 90 % of APA, **APDP** : APD prolongation, **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_{Kr}+I_{Ks}+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, **V/s** : volt per second



Drug

Roxithromycin

Antibiotic used to treat various bacterial infections

Raw data

IC_{50s} (slope) [1]

I_{CaL} : ---- µM (---)
I_{Kr} : 36.5 µM (1.16)
I_{Na} : ---- µM (---)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$

1.314 µM

Britzi et al. (2015) *Ther Drug Monit* **37** 512-515

TdP risk

Redfern [2] : not reported
Kramer [3] : not reported
CredibleMeds [4] : known risk of TdP (class 1)
CiPA [5] : not reported
WP [6] : 2/0 (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 = maximal conductance of channel 'j'
O=open probability of channel 'j'
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where
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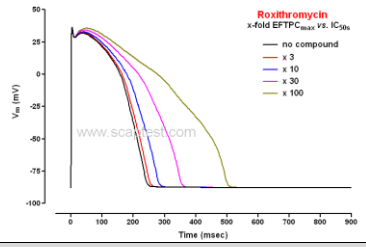
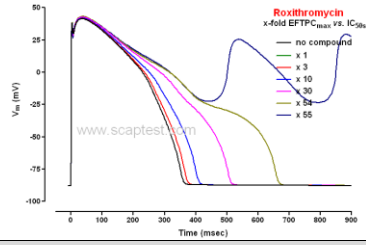
IC index = (AFKr/((AFNaL+AFCaL)/2))*100
where
AFKr, AFNaL and AFCaL = active fraction (%) of the I_{Kr}, I_{NaL} and I_{CaL}

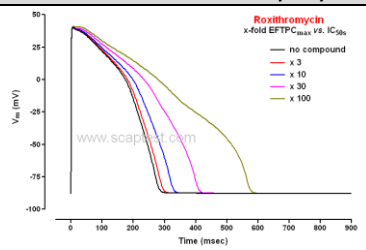
Human epicardial myocytes



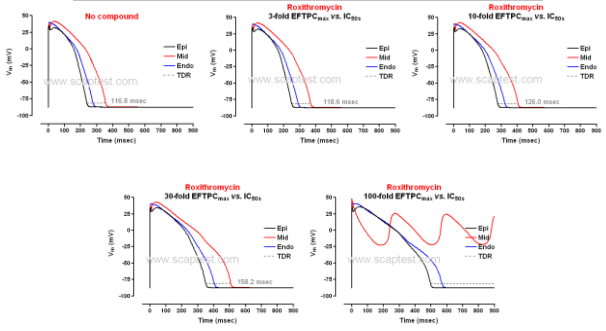
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarization



Reverse use dependence on midmyocardial myocytes

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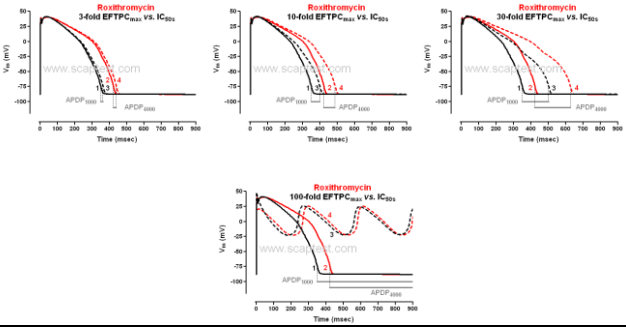
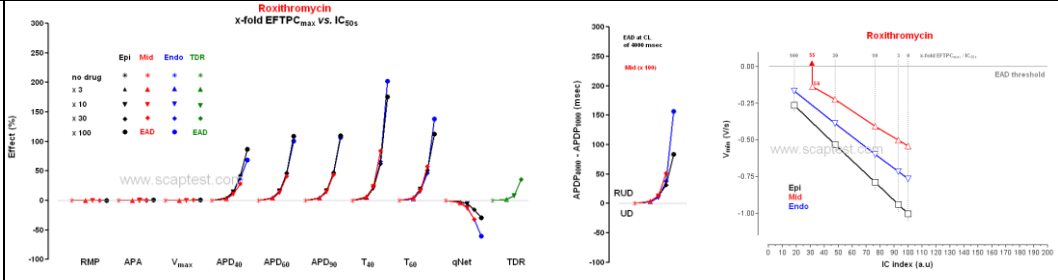


Summary



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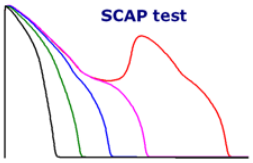

Drug

Sematilide

Potassium voltage-gated cardiac channel ($K_v11.1$) blocker used as class III antiarrhythmic to treat cardiac arrhythmia

Raw data

IC_{50s} (slope) [1]

I_{CaL} : ---- µM (---)
I_{to} : ---- µM (---)
I_{Kr} : 25.0 µM (1.0)
I_{NaL} : ---- µM (---)
I_{Na} : ---- µM (---)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ [1]

4.449 µM

TdP risk

Redfern [2] : class IA or III antiarrhythmic (class 1)
Kramer [3] : not reported
CredibleMeds [4] : not reported
CiPA [5] : not reported
WP [6] : 2/0 (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 = 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'

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

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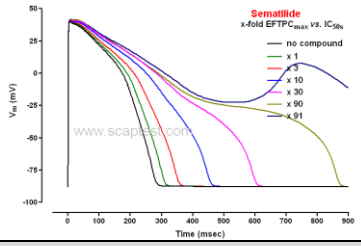
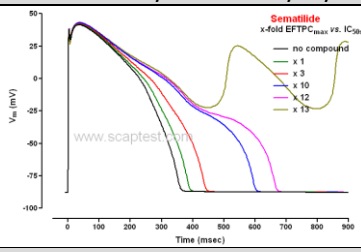
where
$APD_{90}P_x$ = APD_{90} with - APD_{90} without compound at CL x

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

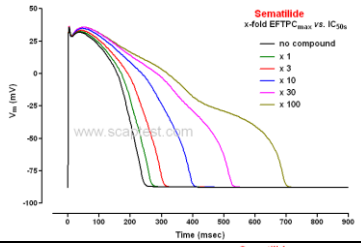
Human epicardial myocytes



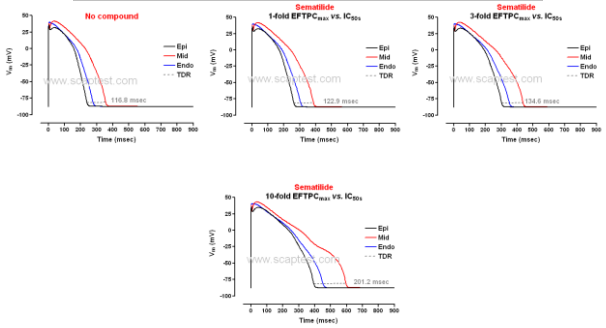
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarization



Reverse use dependence on midmyocardial myocytes

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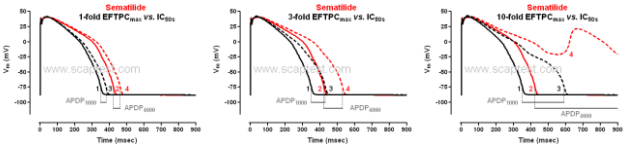
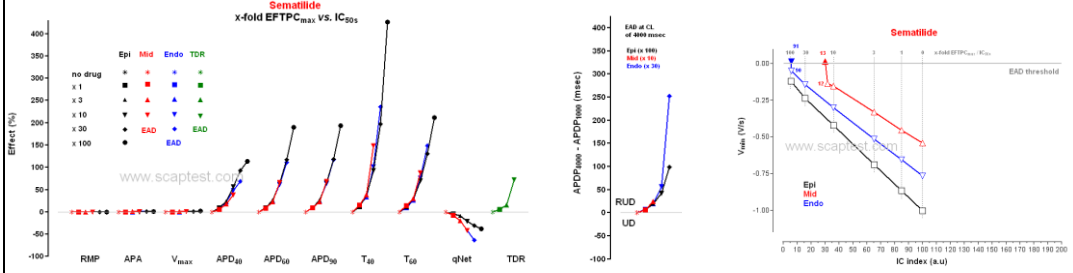


Summary



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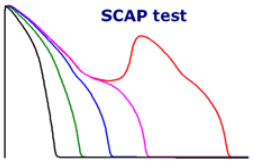

Drug

Sibutramine

Noradrenaline, serotonin and dopamine reuptake inhibitor used to assist with weight loss in obesity
no longer marketed worldwide (Onakpoya et al (2016) *BMC Med.* **14**: 10))

Raw data

IC_{50s} (slope) (1)

I_{CaL} : ---- µM (---)
I_{Kr} : 3.755 µM (1.0)
I_{Na} : ---- µM (---)
I_{KS} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$

0.000161 µM

De Alwis D et al. (2024)
www.hesiglobal.org/cctdatabase

TdP risk

Redfern (2) : not reported
Kramer (3) : not reported
CredibleMeds (4) : no risk of TdP but special risk for patients with long QT
CiPA (5) : not reported
WP (6) : 2/0 (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'

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

g = maximal conductance of channel 'j'
$G_{control,j}$ = drug free maximal conductance of channel 'j'
IC50 = 50% of inhibition of a drug for channel 'j'
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n= hill slope

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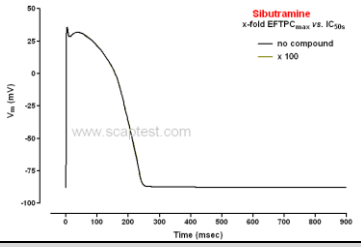
- TDR = APD_{90} mid - APD_{90} epi (at CL of 1000 msec)
- RUD = $APD_{90}P_{x000}$-$APD_{90}P_{1000}$

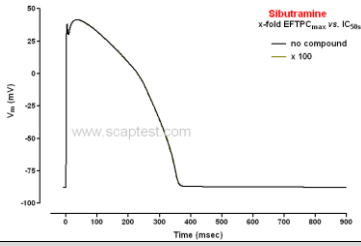
where
$APD_{90}P_x$ = APD_{90} with - APD_{90} without compound at CL x

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

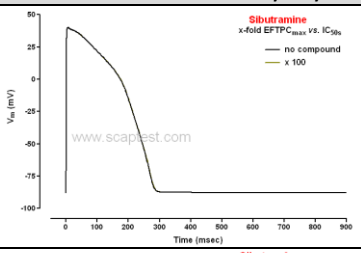
Human epicardial myocytes



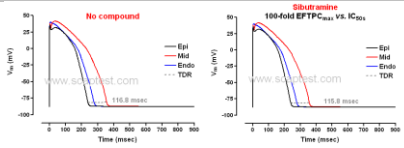
Human midmyocardial myocytes



Human endocardial myocytes

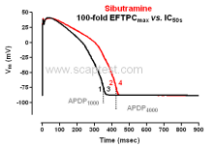


Transmural dispersion of repolarization

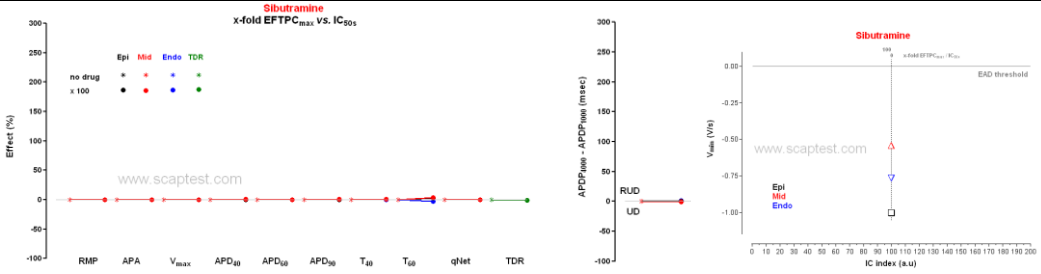


Reverse use dependence on midmyocardial myocytes

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



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1. Polak S et al. (2009) *J. Appl. Toxicol.* **29 :** 183-206
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
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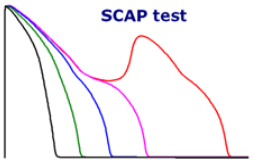
7. O'Hara T et al. (2011) *PLoS Comput. Biol.* **7 :** e1002061_8
8. Mirams GR et al. (2011) *Cardiovasc. Res.* **91 :** 53-61
9. Christophe B & Crumb WJ Jr (2019) *J Pharmacol Toxicol Methods* **96 :** 15-26

Abbreviations

AP : action potential, **APA** : AP amplitude, $\mathbf{APD_{40,60\ or\ 90}}$: 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, $\mathbf{IC_{50}}$: 50% inhibition concentration, **mid** : midmyocardial myocyte, **msec** : millisecond, **mV** : millivolt, **qNet** : integration sum of I_{CaL}+I_{Kr}+I_{Ks}+I_{to}+I_{NaL}+I_{K1}, **RMP** : resting membrane potential, **RUD** : reverse use dependence, $\mathbf{T_{40,60}}$: APD_{90}-APD_{40} or APD_{60} (~triangulation), **TdP** : torsade de pointes , **TDR** : transmural dispersion of repolarization, $\mathbf{V_m}$: membrane voltage, $\mathbf{V_{max}}$: maximal rate of AP rise , $\mathbf{V_{min}}$: minimal rate of AP decrease at EAD take-off voltage, **V/s** : volt per second



Drug	**Sulpiride** Dopamine D_2 receptor antagonist used to treat chronic and acute schizophrenia

Raw data

IC_{50s} (slope) [1]	$EFTPC_{max}$ [1]	TdP risk
I_{CaL} : ---- µM (---) I_{to} : ---- µM (---) I_{Kr} : 805 µM (1.0) I_{NaL} : ---- µM (---) I_{Na} : ---- µM (---) I_{K1} : ---- µM (---) I_{Ks} : ---- µM (---)	0.7082 µM	Redfern [2] : not reported Kramer [3] : not reported CredibleMeds [4] : known risk of TdP (Class 1) CiPA [5] : not reported WP [6] : 1/0 (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

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g_j = maximal conductance of channel 'j'
O=open probability of channel 'j'
V= voltage membrane
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$g_j = g_{control,j}\left[1+\left(\frac{D}{IC50_j}\right)^n\right]^{-1}$

$g_{control,j}$= drug-free maximal conductance of channel 'j'
IC50 = 50% of inhibition of a drug for channel 'j'
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where
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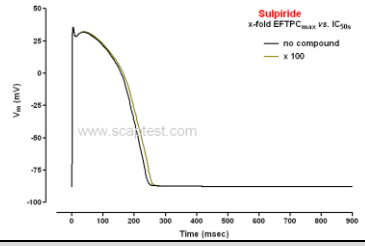
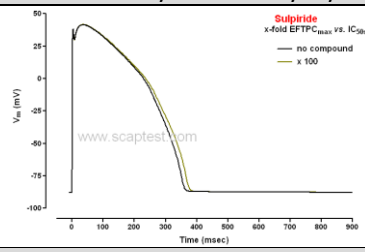
IC index calculation [9]:
IC index = (AFKr/((AFNaL+AFCaL)/2))*100
where
AFKr, AFNaL and AFCaL = active fraction (%) of the I_{Ks}, I_{NaL} and I_{CaL}

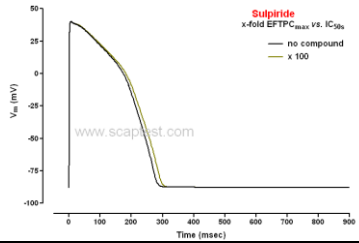
Human epicardial myocytes



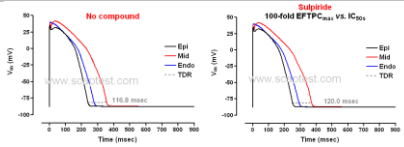
Human midmyocardial myocytes



Human endocardial myocytes

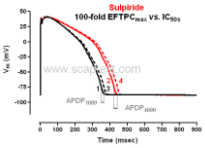


Transmural dispersion of repolarisation

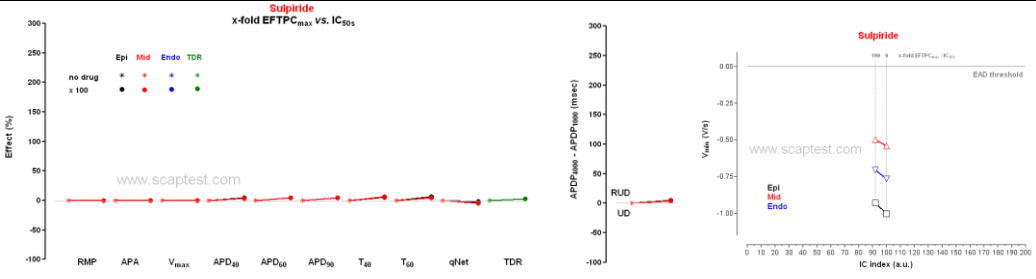


Reverse use dependence on midmyocardial myocytes

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



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1. www.tox-portal.com and www.go.drugbank.com
2. Redfern WS et al. (2003) *Cardiovasc. Res.* **58**: 32-45
3. Kramer J et al. (2013) *Sci.rep.* **3** : 2100
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Abbreviations

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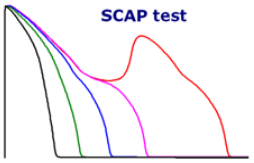

Drug

Telithromycin

Ketolide used as antibiotic to treat community acquired pneumonia of mild to moderate severity

Raw data

IC_{50s} (slope) [1]

I_{CaL} : ---- µM (---)
I_{to} : ---- µM (---)
I_{Kr} : 56.21 µM (0.7)
I_{NaL} : ---- µM (---)
I_{Na} : ---- µM (---)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$

0.5283 µM

Javsicas LH et al (2010) *J. Vet. Pharmacol. Ther.* **33** : 383-388

TdP risk

Redfern [2] : not reported
Kramer [3] : not reported
CredibleMeds [4] : possible risk of TdP (class 2)
CiPA [5] : not reported
WP [6] : 1/1 (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 = maximal conductance of channel 'j'
O=open probability of channel 'j'
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E_{ion} = reversal potential for species of ions which flows through channel 'j'

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

g = maximal conductance of channel 'j'
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D= drug concentration (EFTPC for example)
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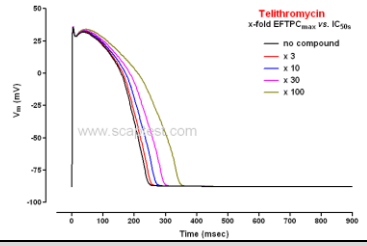
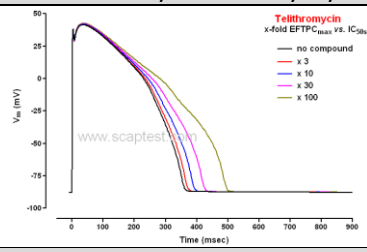
IC index calculation [9]:

IC index = (AFKr/((AFNaL+AFCaL)/2))*100
where
AFKr, AFNaL and AFCaL = active fraction (%) of the I_{Ks}, I_{NaL} and I_{CaL}.

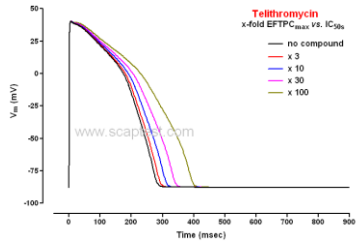
Human epicardial myocytes



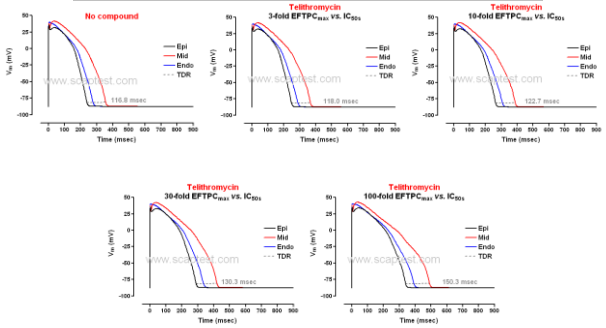
Human midmyocardial myocytes



Human endocardial myocytes

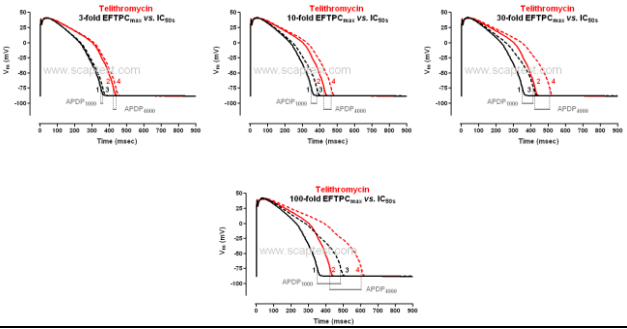


Transmural dispersion of repolarization

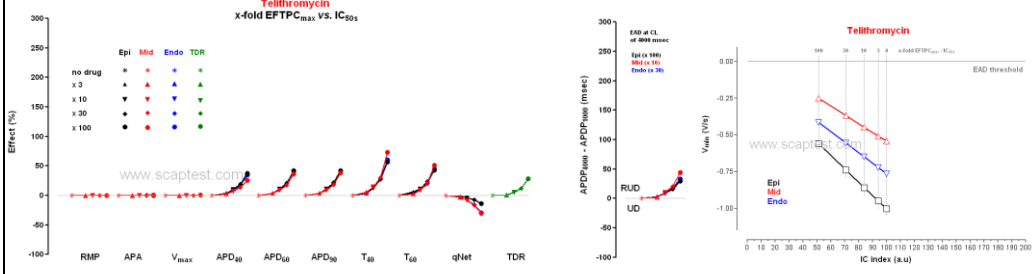


Reverse use dependence on midmyocardial myocytes

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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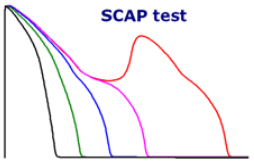

Drug

Tetracaine

Voltage-gated Na^+ ($Na_v1.5$) channel blocker used as local anaesthetic to induce local analgesia in the eyes and skin during medical procedures

Raw data

IC_{50s} (slope) (1)

I_{CaL} : 83.176µM (1.0)
I_{to} : ---- µM (---)
I_{Kr} : 6.310 µM (1.0)
I_{NaL} : 1.950 µM (1.0)
I_{Na} : 1.023 µM (1.0)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ (1)

0.270 µM

TdP risk

Redfern (2) : not reported
Kramer (3) : not reported
CredibleMeds (4) : not reported
CiPA (5) : not reported
WP (6) : not reported

Results

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Effect of drugs on AP (8):
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$I_j = g_j O (V - E_{ion})$; $g_j = g_{j\,control,j}\left[1+\left(\frac{D}{(IC50)_j}\right)^{n_j}\right]^{-1}$

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O=open probability of channel 'j'
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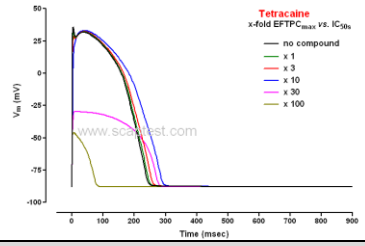
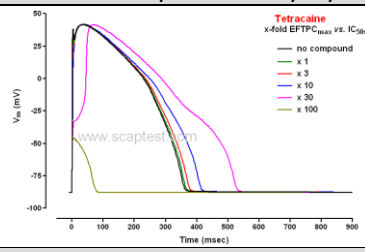
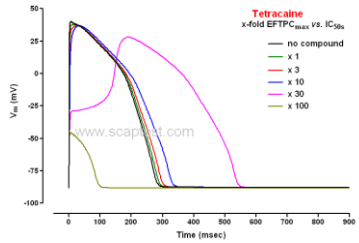


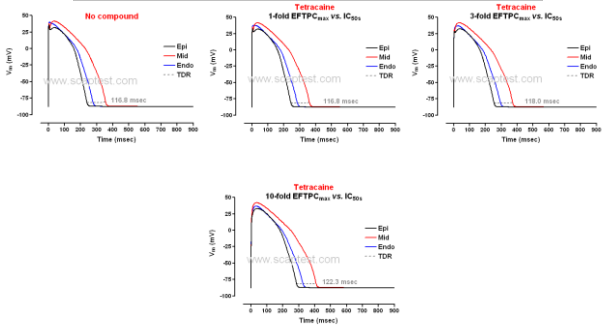
Human midmyocardial myocytes



Human endocardial myocytes

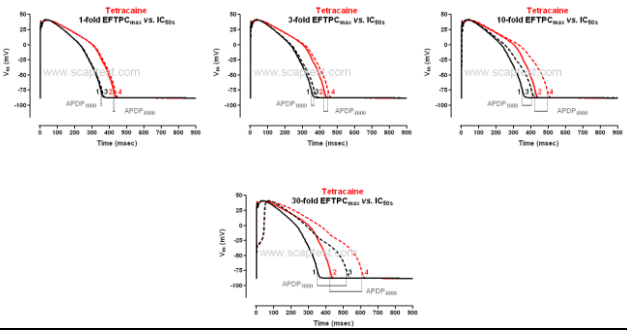


Transmural dispersion of repolarisation

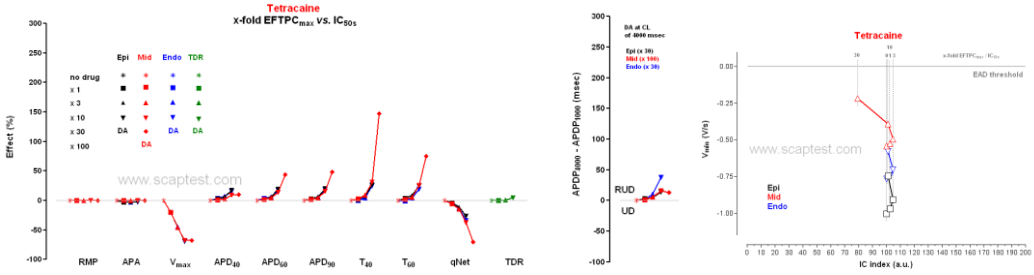


Reverse use dependence on midmyocardial myocytes

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



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1. Watt ED et al. (2022) *J.Pharmacol.Tox.Methods* **118 :** 107213
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
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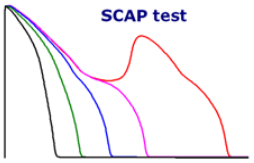
6. Wiśniowska B et al. (2017) *Drug discovery today* **22 :** 10-16
7. O'Hara T et al. (2011) *PLoS Comput. Biol.* **7 :** e1002061_8
8. Mirams GR et al. (2011) *Cardiovasc. Res.* **91 :** 53-61
9. Christophe B & Crumb WJ Jr (2019) *J Pharmacol Toxicol Methods* **96 :** 15-26

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 $I_{CaL}+I_{Kr}+I_{Na}+I_{to}+I_{NaL}+I_{K1}$, **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, **V/s** : volt per second



Drug

Trimipramine

Noradrenaline and serotonin reuptake inhibitor used to treat depression

Raw data

IC_{50s} (slope) [1]

I_{CaL} : ---- µM (---)
I_{to} : ---- µM (---)
I_{Kr} : 2.7 µM (1.0)
I_{NaL} : ---- µM (---)
I_{Na} : ---- µM (---)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$

0.02035 µM

https://e-lactancia.org/media/papers/Trimipramine-DS-APharma2010.pdf

TdP risk

Redfern [2] : not reported
Kramer [3] : not reported
CredibleMeds [4] : possible risk of TdP (class 2)
CiPA [5] : not reported
WP [6] : 1/1 (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 = 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'

$$g_j = g_{control,j}\left[1+\left(\frac{D}{(IC50)_j}\right)^{n_j}\right]^{-1}$$

g = maximal conductance of 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:

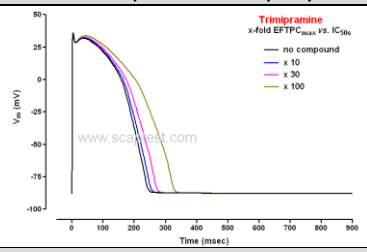
- TDR = APD_{90} mid - APD_{90} epi (at CL of 1000 msec)
- RUD = $APD_{90}P_{4000}$-$APD_{90}P_{1000}$

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

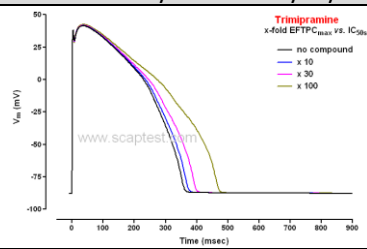
IC index calculation [9]:

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

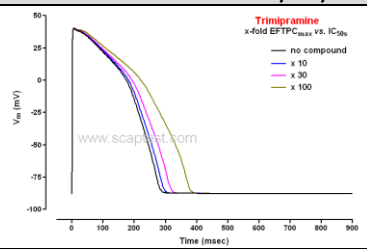
Human epicardial myocytes



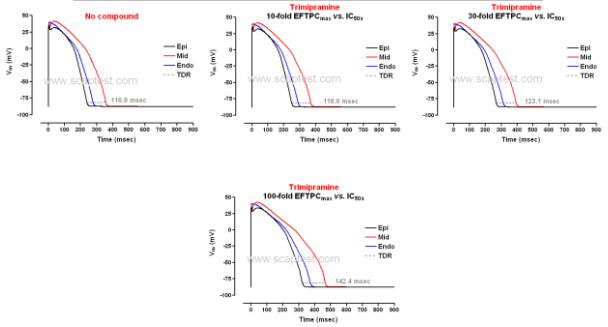
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarization



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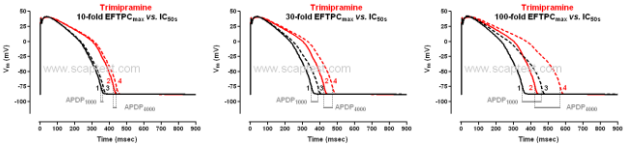
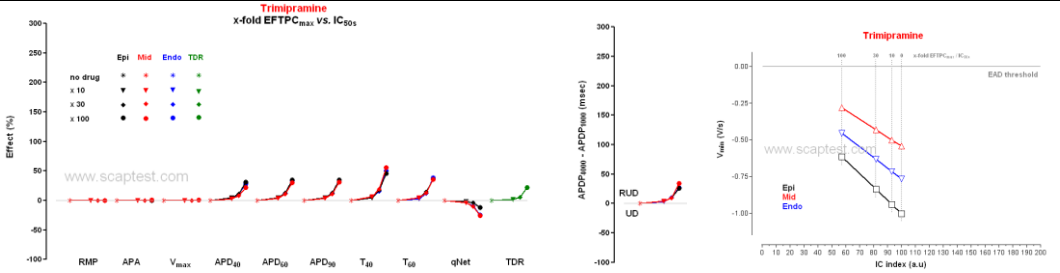


Summary



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3. Kramer J et al. (2013) *Sci.rep.* **3** : 2100
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Abbreviations

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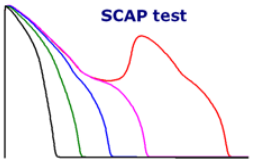

Drug

Venlafaxine

Noradrenaline and serotonin reuptake inhibitor used to treat major depression, generalized or social anxiety disorder and panic disorder

Raw data

IC_{50s} (slope) [1]

I_{CaL} : ---- µM (---)
I_{to} : ---- µM (---)
I_{Kr} : 69.183µM (1.0)
I_{NaL} : ---- µM (---)
I_{Na} : 158.489 µM (1.0)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ [1]

0.081 µM

TdP risk

Redfern [2] : not reported
Kramer [3] : not reported
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$I_j = g_j O (V - E_{ion})$; $g_j = g_{j\,control,j}\left[1+\left(\frac{D}{(IC50)_j}\right)^n\right]^{-1}$

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O=open probability of channel 'j'
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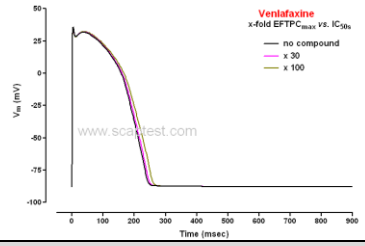
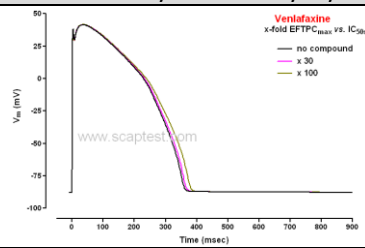
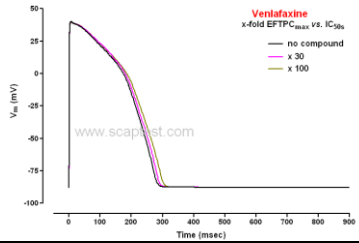


Human midmyocardial myocytes



Human endocardial myocytes



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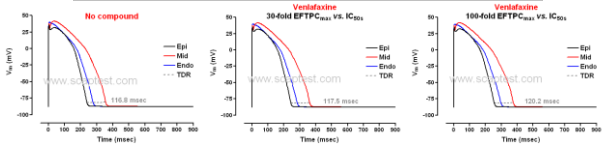

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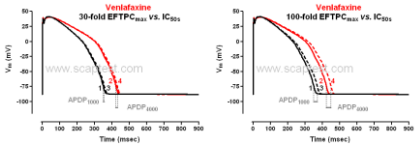

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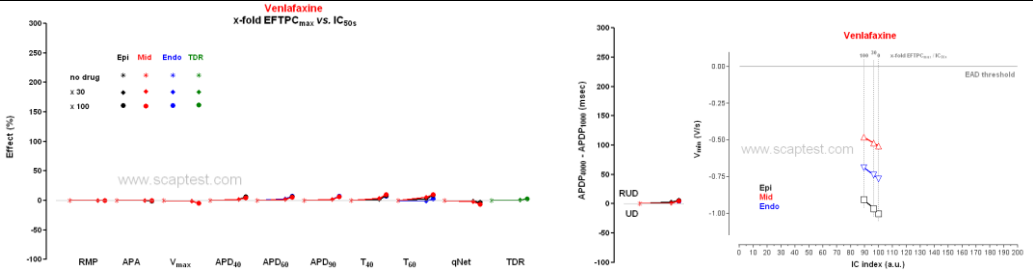

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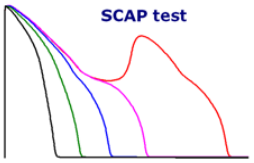

Class I (Known TdP risk) §	I_{Kr} #	I_{CaL} #	I_{Na} #	I_{NaL} #	APA ##	V_{max} ##	APD_{90} ##	T_{60} ##	TDR ##	RUD ##	V_{min} ##	IC_{index} ##	EAD £
Amiodarone	*	*	*		=	=	=	=	=	=	•	98.0	
Astemizole	***	*	*		=	=	••••	••••	••••	1	••••	32.0	x 36
Azithromycin	***			***	=	=	••••	••••	••••	1	••••	50.6	
Bepridil	****	****	***		◦	◦◦◦◦	••••	••••	••	1	••••	10.6	
Chloroquine	***				=	=	••••	••••	••••	1	••••	33.9	x 85
Chlorpromazine	***	***	***		=	◦◦◦	••••	••••	•••	••••	••••	29.5	
Cilostazol	**	*	*		=	◦	••	•••	••	••	•••	55.1	
Ciprofloxacin	***				=	=	••••	••••	••••	1	••••	31.6	x 61
Cisapride	***	*	*		=	=	••••	••••	••••	1	••••	31.7	x 15
Citalopram	***	*	*		=	◦	••••	••••	••••	1	••••	33.2	
Clarithromycin	***				=	=	••••	••••	••••	1	••••	31.6	x 48
Disopyramide	***	*	*		=	◦	••••	••••	••••	1	••••	31.4	x 48
Dofetilide	***	*	*		=	=	••••	••••	••••	1	••••	32.1	x 29
Domperidone	***		*		=	=	••••	••••	••••	1	••••	33.1	x 13
Donepezil	**	*	*		=	=	•	••	•	••	••	70.3	
Dronedarone	***	**	**		=	◦	••••	••••	••••	1	••••	29.2	
Droperidol	***	*	*		=	=	••••	••••	••••	1	••••	33.6	x 8
Erythromycin	***				=	=	••••	••••	••••	1	••••	33.7	x 10
Flecainide	***	*	**		=	◦◦◦	••••	••••	••••	1	••••	29.7	x 7
Fluconazole	***				=	=	••••	••••	••••	1	••••	31.7	x 7
Gatifloxacin	***				=	=	••••	••••	••••	1	••••	32.0	x 7
Grepafloxacin	***				=	=	••••	••••	••••	1	••••	31.6	x 37
Halofantrine	***	**	*		=	=	••••	••••	••••	1	••••	25.8	x 7
Haloperidol	***	*	*		=	=	••••	••••	••••	1	••••	32.2	x 20
Hydrochloroquine	****	**			=	=	••••	••••	••••	1	••••	35.4	x 12
Ibutilide	***	*	*		=	=	••••	••••	••••	1	••••	33.7	x 0.3
Ivabradine	**	*	*		=	=	•	••	•	•	••	73.3	
Levofloxacin	***				=	=	••••	••••	••••	1	••••	32.2	x 30
Mesoridazine	***	*	*	*	=	◦	••••	••••	••••	1	••••	35.0	x 0.4
Methadone	***	*	*		=	◦	••••	••••	••••	1	••••	31.3	x 17
Moxifloxacin	****	****	**		◦	◦◦◦	••••	•••	=	••••	••••	14.8	
Nifekalant	***				=	=	••••	••••	••••	1	••••	31.8	x 27
Ondansetron	***	**		**	=	=	••••	••••	••••	1	••••	30.6	x 14
Pentamidine	*				=	=	•	••••	••	◦	=	99.5	
Pimozide	***	*	*		=	=	•••	•••	••	•••	••••	45.6	
Procainamide	****	****	****		2	2	2	2	2	2	2	8.7	
Quinidine	***	**	*		=	◦	••••	••••	••••	1	••••	27.4	x 0.8
Roxithromycin	***				=	=	••••	••••	••••	1	••••	31.6	x 55
Sertindole	***	*	*		=	=	••••	••••	••••	••••	••••	32.2	x 31
Sotalol	****	****	*		◦	◦	••••	•••	◦◦	••••	••••	23.7	
Sparfloxacin	****	***	*		=	=	••••	••••	••••	1	••••	18.9	
Sulpiride	*				=	=	=	=	=	=	•	91.9	
Terfenadine	***	*	*		=	=	••••	••••	••••	1	••••	31.6	x 12
Terodiline	***	**	*		=	◦	••••	••••	••••	1	••••	26.7	x 16
Thioridazine	***	*	**		=	◦◦◦	••••	••••	••••	1	••••	36.9	x 2
Vandetanib	***				=	=	••••	••••	••••	1	••••	34.2	x 8

§ : Crediblemeds classification of compound TdP risk (08/2024)

: Active fraction of I_{Kr}, I_{CaL}, I_{Na} or I_{NaL} cardiac current calculated at an $EFTPC_{max}/IC_{50s}$ ratio of 100-fold in absence of EAD or at the last $EFTPC_{max}/IC_{50s}$ ratio (x-fold-1) before the presence of an EAD: 0 to 20 % (****), 20 to 50 % (***), 50 to 80 % (**) and 80 to 99.9 % (*). Absence of (*) in case of an active fraction of 100 %.

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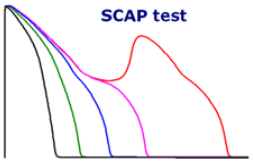

Class II (Possible TdP risk)§	I_{Kr} #	I_{CaL} #	I_{Na} #	I_{NaL} #	APA ##	V_{max} ##	APD_{90} ##	T_{60} ##	TDR ##	RUD ##	V_{min} ##	IC_{index} ##	EAD £
Alfuzosin	*	*	*		=	=	=	=	=	=	=	99.8	
Asenapine	*				=	=	•	•	•	•	••	81.1	
Atomoxetine	**				=	=	••	••	•	••	••	68.0	
Bedaquiline	***				=	=	••••	••••	••••	1	••••	33.3	
Bosutinib	***				=	=	••••	••••	••••	1	••••	32.1	x 29
Ceritinib	***				=	=	••••	••••	••••	1	••••	33.0	x 15
Clozapine	***	***	**		◦	◦◦	••••	•••	••	••••	••••	37.6	
Crizotinib	*				=	=	•	•	•	•	••	81.7	
Dasatinib	*	*	*		=	=	•	=	=	•	••	91.0	
Desipramine	****	****	****		2	2	2	2	2	2	2	20.2	
Dolasetron	****		**		=	◦◦	••••	••••	••••	1	••••	32.7	x 35
Granisetron	*	**			=	=	•	•	=	=	•	93.0	
Imatinib	**				=	=	••	•••	••	•••	•••	51.2	
Imipramine	***	***	***		=	◦◦◦◦	••••	••••	•••	••••	••••	33.9	
Isradipine	*	****	*	*	◦	•	◦◦	=	◦	=	◦◦	189	
Ketanserin	***				=	=	••••	••••	••••	1	••••	31.8	x 78
Lapatinib	***	*	*		=	=	••••	••••	••••	1	••••	31.9	x 55
Lopinavir	****	****			◦	•	••••	••••	•••	1	••••	7.1	
Maprotiline	****	***	****	****	2	2	2	2	2	2	2	83.0	
Nicardipine	****	****	***		◦◦	◦◦◦	••••	•	◦◦	••••	••••	30.4	
Nilotinib	***	*	*		=	=	••••	••••	••••	1	••••	29.5	x 17
Nortriptyline	***	***	****	***	2	2	2	2	2	2	2	99.1	
Ofloxacin	**				=	=	••	••	•	•	•••	62.0	
Paliperidone	****	*	*		=	=	••••	••••	••••	1	••••	32.9	x 25
Palonosetron	*	*	*		=	=	•	•	•	•	••	81.1	
Pitolisant	***	*	*		=	=	•••	•••	••	•••	••••	48.3	
Promethazine	**				=	=	•	•	•	•	••	74.3	
Ribociclib	***		**		=	◦	••••	••••	••••	1	••••	32.7	x 33
Rilpivirine	**				=	=	••	•••	••	••	•••	50.5	
Saquinavir	**	****	***		◦	◦◦◦	•	◦	◦◦◦◦	◦	•••	111	
Sunitinib	***	*	*		=	=	•••	•••	••	•••	•••	48.7	
Tamoxifen	***				=	=	••••	••••	••••	1	••••	31.7	x 94
Telithromycin	**				=	=	••	•••	••	•••	•••	51.1	
Tolterodine	***		*		=	=	••••	••••	••••	1	••••	32.0	x 28
Trimipramine	**				=	=	••	••	••	••	••	57.0	
Vardenafil	*	*	*		=	=	=	=	=	=	=	100	
Venlafaxine	*		*		=	=	•	•	=	=	•	89.5	
Vernakalant	****	****	****	****	2	2	2	2	2	2	2	44.8	

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[1] EAD observed at CL of 4000 msec preventing the RUD calculation

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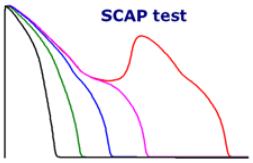

Class III (Conditional TdP risk) [§]	I_{Kr} [#]	I_{CaL} [#]	I_{Na} [#]	I_{NaL} [#]	APA [##]	V_{max} [##]	APD_{90} [##]	T_{60} [##]	TDR [##]	RUD [##]	V_{min} [##]	IC_{index} [##]	EAD [£]
Amitriptyline	**	***	**	**	◦	◦◦	••	••	•	◦	•••	128	
Clomipramide	***	*	*		=	◦	••••	••••	••••	1	••••	35.0	
Diltiazem	**	****	**		◦	◦◦	••	•	◦◦	•	•••	101	
Diphenhydramine	**	*	*		=	◦	••	••	•	•	•••	60.9	
Doxepin	**				=	=	••	••	•	••	•••	60.4	
Famotidine	*				=	=	=	=	=	=	=	98.6	
Fluoxetine	**	**	*		=	=	••	••	•	•	•••	67.1	
Fluvoxamine	****	****	**		◦	◦◦	••••	•••	=	••••	••••	21.8	
Furosemide	**				=	=	••	•••	••	•••	•••	51.6	
Galantamine	*				=	=	=	=	=	=	=	99.6	
Hydroxyzine	***	*	***	*	=	◦◦◦◦	••••	••••	••••	1	••••	34.4	x 90
Ketoconazole	***		*		=	◦	••••	••••	••••	1	••••	32.5	x 43
Loperamide	*		*		=	=	•	=	=	•	•	89.3	
Metoclopramide	***				=	=	••••	••••	••••	1	••••	36.7	
Metronidazole	****	****	****		2	2	2	2	2	2	2	12.8	
Nelfinavir	**		*		=	◦	••	••	•	••	•••	63.9	
Olanzapine	***		**		=	◦◦	••••	••••	••••	1	••••	33.1	x1.4
Paroxetine	**	*	*		=	◦	••	••	•	••	•••	65.9	
Piperacillin	****	****	****		2	2	2	2	2	2	2	4.8	
Propafenone	****	****	***	***	◦	◦◦◦◦	••••	•••	◦◦	••••	••••	34.5	
Quetiapine	****	****			◦	•	••••	••••	••	1	••••	12.8	
Quinine	***	**	**	***	=	◦◦	••••	••••	••••	1	••••	44.9	x 5
Ranolazine	***			***	=	=	••••	••••	••••	1	••••	43.1	x 12
Risperidone	**	*	*		=	=	••	••	••	••	•••	56.9	
Sertraline	****	****	****		2	2	2	2	2	2	2	0.6	
Solifenacin	***	*	*		=	◦	•••	•••	••	•••	•••	48.9	
Voriconazole	***	***	**		◦	◦◦	•••	••	•	•	•••	58.1	
Ziprasidone	***		*		=	=	••••	••••	••••	•••	••••	31.6	x 72

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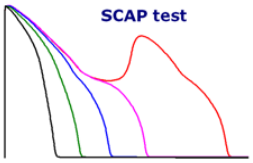

Class IV (No TdP risk) §	I_{Kr} #	I_{CaL} #	I_{Na} #	I_{NaL} #	APA ##	V_{max} ##	APD_{90} ##	T_{60} ##	TDR ##	RUD ##	V_{min} ##	IC_{index} ##	EAD £
Ajmaline	***	*	**		=	∘∘	••••	••••	••••	[1]	••••	31.6	x 93
Alosetron	*				=	=	•	•	=	•	•	87.3	
Ambrisentan	*	*	*		=	=	=	=	=	=	=	97.7	
Amlodipine	****	****	***		∘∘	∘∘∘∘	••••	•	∘∘	••••	••••	26.3	
Aspirin	*				=	=	=	=	=	=	=	99.2	
Atenolol	*				=	=	•	•	=	=	•	91.4	
Bupivacaine	***	**	****	****	2	2	2	2	2	2	2	80.7	
Carbamazepine		***	***	****	∘	∘∘∘∘	∘	∘	∘∘∘∘	∘∘	∘	539	
Carvedilol	***				=	=	•••	•••	••	•••	•••	49.9	
Cetirizine	*				=	=	=	=	=	=	=	97.7	
Chlorpheniramine	*				=	=	=	•	=	=	•	91.5	
Darifenacin	***	*	*		=	∘	••••	••••	••••	••••	••••	36.9	
Darunavir	**		***		=	∘∘∘	•	••	•	•	••	77.4	
Dasabuvir	*				=	=	=	=	=	=	=	97.0	
Desvenfalaxine	***		***		=	∘∘∘∘	•••	•••	••	••••	•••	49.4	
Diazepam	*	*	*		=	=	=	=	=	=	=	101	
Digoxin	***				=	=	••••	••••	••••	[1]	••••	31.6	x 93
Doxorubicin	**				=	=	•••	••	•••	••	•••	68.3	
Duloxetine	**	**	*		=	∘	•	•	=	=	••	91.1	
Eltrombopag	***		*		=	=	••••	••••	••••	[1]	••••	33.3	x 12
Everolimus	*		*		=	=	=	=	=	=	=	98.7	
Felodipine	*	***	*	*	∘	=	∘	∘	∘∘	∘∘	∘	164	
Fexofenadine	*				=	=	•	=	•	=	•	93.6	
Irbesartan	**				=	=	••	••	••	•	••	67.0	
Lacosamide	*	****	****		2	2	2	2	2	2	2	177	
Lamivudine	**	****	***		∘	∘∘∘	••	∘	∘∘∘∘	=	•••	98.8	
Lamotrigine	***	**	****		=	∘∘∘∘	••••	••••	••••	[1]	••••	41.4	x 14
Levocetirizine	*				=	=	=	=	=	=	•	94.1	
Lidocaine				****	=	=	∘	=	∘	∘	∘	197	
Linezolid	****	****	***		∘∘	∘∘∘∘	••••	∘	∘∘	••••	••••	31.8	
Loratadine	*	*	*		=	=	=	=	=	=	=	99.9	
Mefloquine	**				=	=	•••	•••	•••	••	•••	59.7	
Metoprolol	**	*	****	**	=	∘∘∘∘	=	•	∘∘	∘∘	=	116	
Mexiletine				****	=	=	∘	=	∘	∘	∘	198	
Milrinone	*				=	=	=	=	=	=	=	96.4	
Mitoxantrone	*	**	*		=	∘	=	=	∘	∘∘	=	128	
Mizolastine	***				=	=	••••	••••	••••	[1]	••••	31.6	x 88
Nebivolol	**		*		=	=	•	•	•	•	••	77.1	
Nifedipine	*	****	*		∘	=	∘	•	∘	••	•••	190	
Oseltamivir	*	*	*		=	=	=	=	=	=	•	95.2	
Oxybutynin	*	*			=	=	=	=	=	=	=	100	
Phenytoin	***	****	****		2	2	2	2	2	2	2	48.1	
Primidone	**		***		=	∘∘∘	••	••	•	••	•••	62.0	
Propranolol	*	*			=	=	•	•	=	=	•	91.2	
Raltegravir	*	**	*		=	∘	=	=	=	=	•	103	
Ribavirin	***	****	**		∘	∘∘∘	•••	••	∘	•••	••••	43.6	
Sildenafil	*	*	*		=	=	•	•	•	•	•	84.4	
Silodosin	*	*	*		=	=	•	•	=	•	•	89.5	
Tadalafil	*		*		=	∘	•	•	•	•	•	88.0	
Verapamil	****	****	*		∘	∘	••••	••••	∘	••••	••••	7.7	

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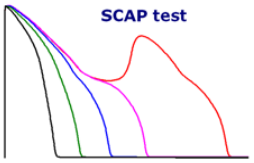


Class V (not reported) §	I_{Kr} #	I_{CaL} #	I_{Na} #	I_{NaL} #	APA ##	V_{max} ##	APD_{90} ##	T_{60} ##	TDR ##	RUD ##	V_{min} €	IC_{index} ##	EAD £
Almokalant	***				=	=	••••	••••	••••	1	••••	31.9	x 48
Alvimopan	*	*	*		=	=	=	=	=	◦	=	109	
Aprindine	***				=	=	••••	••••	••••	1	••••	32.5	x 2.1
Azimilide	***				=	=	••••	••••	••••	1	••••	31.6	x 13
Ceftriaxone	****	****	****		◦◦	◦◦◦◦	••••	•	◦◦◦◦	•••	••••	30.4	
Cibenzoline	***		*	**	=	◦	••••	••••	••••	1	••••	36.2	x 8
Deferasirox	*	*	***		=	◦◦◦	=	•	=	=	=	102	
Dobutamine +	*	*	*		=	=	•	•	•	•	•	86.0	
Doripenem	***	****	****		2	2	2	2	2	2	2	82.6	
E-4031	***	*	*		=	=	••••	••••	••••	1	••••	37.6	x 7
Ebastine	*				=	=	=	=	=	=	=	98.1	
Encainide	***		**		=	◦◦	•••	•••	••	••••	•••	47.0	
Etravirine	*		*		=	=	=	=	=	=	=	99.8	
Fenspiride	***				=	=	••••	••••	••••	1	••••	31.6	x 47
Gefitinib	***				=	=	••••	••••	••••	1	••••	32.5	x 26
Levosimendan	*	*	*		=	=	=	•	=	=	•	95.6	
Manidipine	*	*	*	*	=	=	=	=	=	=	=	101	
Maraviroc	**		*		=	=	•	•	•	•	••	78.4	
Mepivacaine	***		***		=	◦◦◦◦	••••	••••	••••	1	••••	36.3	x 24
Mibefradil	**	***	*		◦	=	•	•	◦◦	◦	••	101	
Nilvadipine	*	****	*	*	◦	=	◦	=	◦	◦	••	188	
Nimodipine	*	**			=	=	=	◦	=	◦◦	•	129	
Nisoldipine	*	*			=	=	=	=	=	=	=	106	
Nitrendipine	*	****	*		◦	=	◦	◦	◦◦	◦	•	173	
Omecamtiv mecarb	*	*	*		=	◦	•	•	•	•	•	84.9	
Pentobarbital	**	***	*		◦	◦	•	=	◦	◦◦	◦	111	
Prenylamine	***	*	*		=	◦	••••	••••	••••	1	••••	28.9	x 51
Procaine	***		**	**	=	◦◦	••••	••••	••••	1	••••	36.6	x 6
Ritonavir	****	****		***	◦	•	••••	••••	◦	••••	••••	65.4	
Ropivacaine	***		***	***	=	◦◦◦◦	••••	••••	••••	1	••••	48.9	x 61
Rufinamide		****			◦	•	◦	•	=	•	••	192	
Sematilide	***				=	=	••••	••••	••••	1	••••	31.9	x 13
Sibutramine +	*				=	=	=	=	=	=	=	99.6	
Sitaglitin	**	**	*		=	=	•	=	•	=	•	90.2	
Tedisamil	***				=	=	••••	••••	••••	1	••••	34.0	x5.5
Telbivudine	****	***	***		◦	◦◦◦◦	••••	•••	••	••••	••••	27.9	
Tetracaine	****	**	****	****	2	2	2	2	2	2	2	46.1	
Vanoxerine	****	****	****	****	2	2	2	2	2	2	2	13.3	

§ : Crediblemeds classification of compound TdP risk (08/2024)

: Active fraction of I_{Kr}, I_{CaL}, I_{Na} or I_{NaL} cardiac current calculated at an $EFTPC_{max}/IC_{50s}$ ratio of 100-fold in absence of EAD or at the last $EFTPC_{max}/IC_{50s}$ ratio (x-fold-1) before the presence of an EAD: 0 to 20 % (****), 20 to 50 % (***), 50 to 80 % (**) and 80 to 99.9 % (*). Absence of (*) in case of an active fraction of 100 %.

: Effect measured on the midmyocardial myocyte at an $EFTPC_{max}/IC_{50s}$ ratio of 100-fold in absence of EAD or at the last $EFTPC_{max}/IC_{50s}$ ratio (x-fold-1) before the presence of an EAD: -5 to 5 % (=), -5 to -20 % (◦), -20 to -40 % (◦◦), -40 to -60 % (◦◦◦), > -60 % (◦◦◦◦), 5 to 20 % (•), 20 to 40 % (••), 40 to 60 % (•••) and > 60 % (••••)

€ : IC index: Ion Channel inhibition index calculated at an $EFTPC_{max}/IC_{50s}$ ratio of 100-fold in absence of EAD or at the last $EFTPC_{max}/IC_{50s}$ ratio (x-fold-1) before the presence of an EAD (see page 4 for calculation)

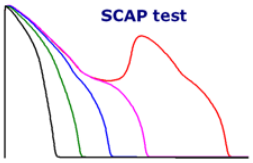
£ : First $EFTPC_{max}/IC_{50s}$ ratio (x-fold) inducing an EAD

[1] EAD observed at CL of 4000 msec preventing the RUD calculation

[2] Depolarisation abnormality

\+ Compounds with special risk for patient with congenital long QT

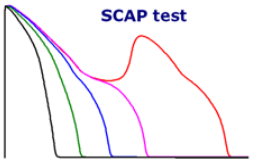
Red color: Compounds described in the present zenodo file, other compounds already described in a previous zenodo file (doi: 10.5281/zenodo.7541554)



Drugs:

Alosetron	6	Digoxin	19	Manidipine	32	Ribociclib	45
Aprindine	7	Doxepin	20	Maprotiline	33	Ropivacaine	46
Asenapine	8	Felodipine	21	Mepivacaine	34	Rilpivirine	47
Atomoxetine	9	Fenspiride	22	Mesoridazine	35	Roxithromycin	48
Bedaquiline	10	Fluconazole	23	Metoclopramide	36	Sematilide	49
Bosutinib	11	Furosemide	24	Mizolastine	37	Sibutramine	50
Bupivacaine	12	Galantamine	25	Nifekalant	38	Sulpiride	51
Carbamazepine	13	Granisetron	26	Nilvadipine	39	Telithromycin	52
Carvedilol	14	Grepafloxacin	27	Nortriptyline	40	Tetracaine	53
Ceritinib	15	Imatinib	28	Oseltamivir	41	Trimipramine	54
Clomipramide	16	Irbesartan	29	Pilotisant	42	Venlafaxine	55
Crizotinib	17	Isradipine	30	Procaine	43		
Dasabuvir	18	Loperamide	31	Promethazine	44		

Summary tables:



Some of these data were also described in the following papers:

Christophe B**.** (2022)
Occurrence of early afterdepolarization under healthy or hypertrophic cardiomyopathy conditions in the human ventricular endocardial myocyte: *in silico* study using 109 torsadogenic or non-torsadogenic compounds.
Toxicol. Appl. Pharmacol., **438** : 115914

Christophe B. & Crumb W.J. Jr (2019)
Impact of disease state on arrhythmic event detection by action potential modeling in cardiac safety pharmacology
J. Pharmacol. Toxicol. Methods, **96** : 15-26

Christophe B. (2015)
In silico study of transmural dispersion of repolarisation in non-failing human ventricular myocytes: contribution to cardiac safety pharmacology
Br. J. Pharm. Res., **7** : 2, 88-101

Christophe B. (2013)
Simulation of early-afterdepolarisation in nonfailing human ventricular myocytes: can this help cardiac safety pharmacology ?
Pharmacol. Rep., **65** : 5, 1281-1293

The implementation of this database is still in progress: In addition to the 50 drugs described in this file, 150 other drugs were already described in the following zenodo file: (Christophe B. (2023) Safe cardiac action potential test (www.scaptest.com): a database describing the *in silico* cardiac safety profile of drugs and their propensity to induce early afterdepolarization. doi:10.5281/zenodo.7541554)

New results are available at www.scaptest.com (please, create an account for free to see the results).

Comments/suggestions regarding this database are to be sent to bchristophe@scaptest.com

Electronic citation:

Christophe B. (2024) Safe cardiac action potential test (www.scaptest.com): a database describing the *in silico* cardiac safety profile of drugs and their propensity to induce early afterdepolarization Part II: description of 50 additional drugs. doi:10.5281/zenodo.13913353