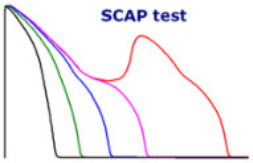

Safe cardiac action potential test (www.scaptest.com) : a database describing the *in silico* cardiac safety profile of drugs and their propensity to induce early afterdepolarization

Bernard **Christophe**, PhD

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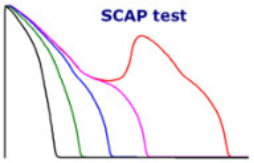
doi: 10.5281/zenodo.7541554

January 2023 – version 1.0 – 150 drugs described

Electronic citation:

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



Aim of the database

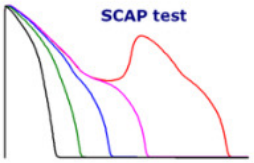
The aim of the present database is to describe the *in silico* cardiac safety profile of drugs and their propensity to induce early afterdepolarization. This is based on the study of the effects of drugs on the non-failing human ventricular myocyte (endo-, mid- and epicardial subtypes) action potential 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

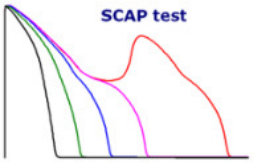
- Conductance of the channel (g_j) modified by a scaling factor ranked from 1 (no inhibition) to 0 (full inhibition) determined from the tested $EFTPC_{max}/IC_{50s}$ ratio.

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

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

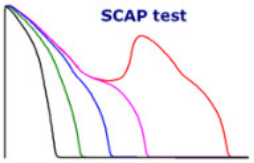
- Calculation of action potential duration prolongation ($APD_{90}P$) induced by a compound (*vs.* absence of compound) on the midmyocardial myocytes at CL of 1000 and 4000 msec
- RUD = $APD_{90}P_{4000}$-$APD_{90}P_{1000}$ where

$APD_{90}P_x$ = 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

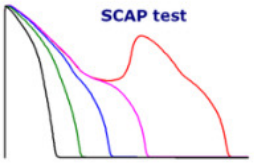
- **Redfern** TdP risk classification : (Cardiovasc Res 2003, 58 : 32-45)
    - Class 1 (class IA or III anti-arrhythmics with large but acceptable TdP risk)
    - Class 2 (compounds withdrawn from the market due to unacceptable TdP risk)
    - Class 3 (compounds with numerous TdP reports)
    - Class 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

Ajmaline

Voltage-gated Na^+ channel ($Na_v1.5$) blocker used as class IA antiarrhythmic to treat tachycardia

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 71.0 µM (1.0)
I_{Kr} : 1.04 µM (1.0
I_{Na} : 8.2 µM (1.0)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ [1]

0.025 µM

TdP risk

Redfern [2] : large but acceptable TdP risk (class 1)
Kramer [3] : not reported
CredibleMeds [4] : not reported
CiPA [5] : not reported
WP [6] : 8/0 (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_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:

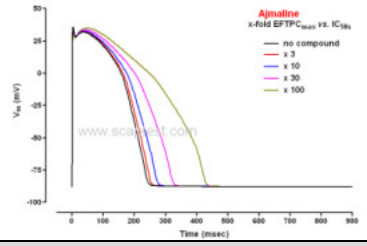
- TDR = APD_{90} mid - APD_{90} epi (at CL of 1000 msec)
- RUD = $APD_{90}P_{x000}$- $APD_{90}P_{1000}$

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

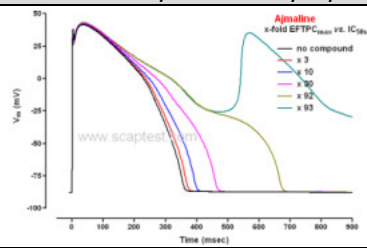
IC index calculation [9]:

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

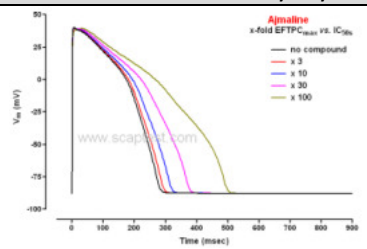
Human epicardial myocytes



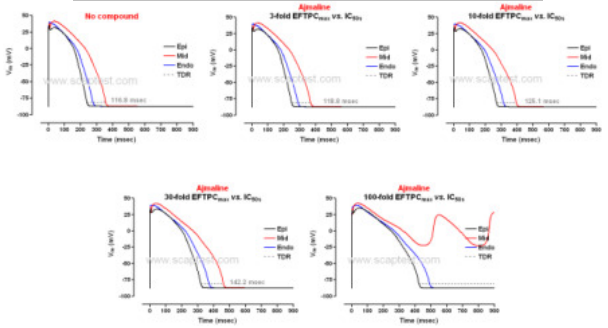
Human midmyocardial myocytes



Human endocardial myocytes

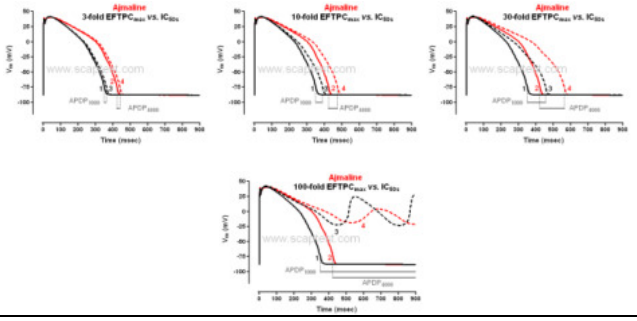


Transmural dispersion of repolarisation

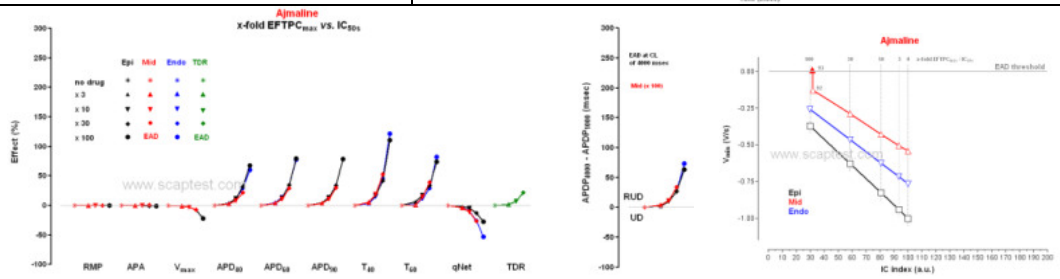


Reverse use dependence on midmyocardial myocytes

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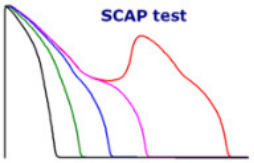
7. O'Hara T et al. (2011) *PLoS Comput. Biol.* **7** : e1002061 8
8. Mirams GR et al. (2011) *Cardiovasc. Res.* **91** : 53-61
9. Christophe B & Crumb WJ Jr (2019) *J Pharmacol Toxicol Methods* **96** : 15-26

Abbreviations

AP : action potential, **APA** : AP amplitude, **$APD_{40, 60 or 90}$** : 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, **$T_{40,50}$** : APD_{90}-APD_{40} or APD_{50} (~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

Alfuzosin

α_1-adrenoceptor antagonist used to treat benign prostatic hypertrophy

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 199.5 µM (1.0)
I_{Kr} : 125.9 µM (1.0)
I_{Na} : 199.5 µM (1.0)
I_{Ks} : 125.9 µM (1.0)
I_{to} : 1000.0 µM (1.0)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ [1]

0.00463 µM

TdP risk

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

$$I_j = g\,O\,(V - E_{ion})$$

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:

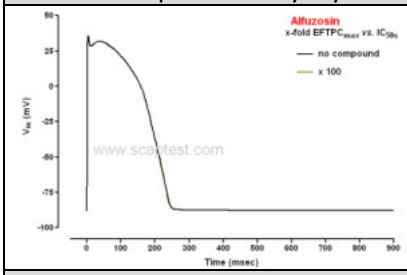
- TDR = APD_{90} mid - APD_{90} epi (at CL of 1000 msec)
- RUD = $APD_{90}P_{x000}$- $APD_{90}P_{1000}$

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

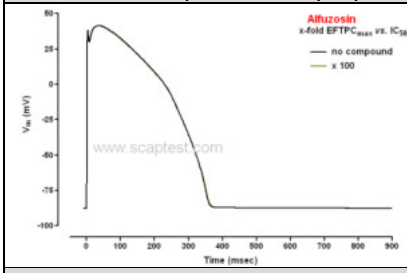
IC index calculation [9]:

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

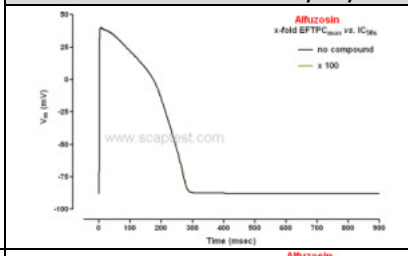
Human epicardial myocytes



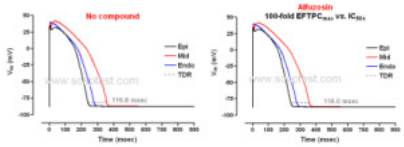
Human midmyocardial myocytes



Human endocardial myocytes

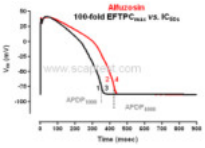


Transmural dispersion of repolarisation

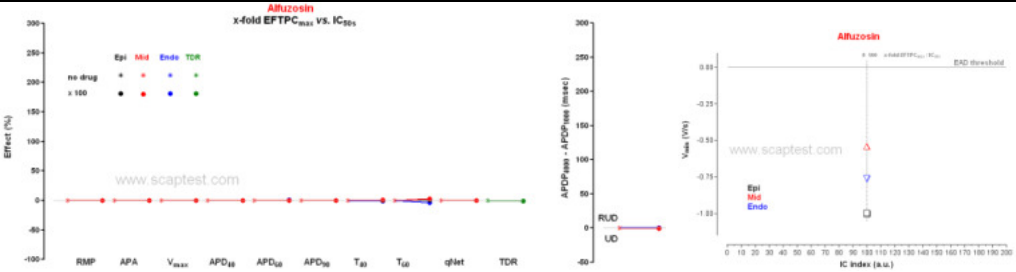


Reverse use dependence on midmyocardial myocytes

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
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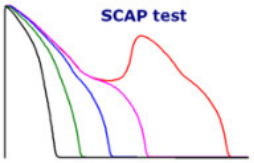

Drug

Almokalant

Rapid delayed rectifier voltage-gated K^+ current (K_v11.1) blocker used as class III antiarrhythmic to treat arrhythmia

Raw data

IC_{50s} (slope) [1]

I_{CaL} : ---- µM (---)
I_{to} : ---- µM (---)
I_{Kr} : 3.66 µM (1.16)
I_{NaL} : ---- µM (---)
I_{Na} : ---- µM (---)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ [1]

0.15 µM

TdP risk

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

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

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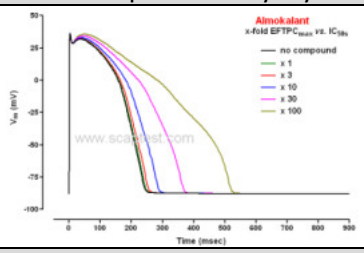
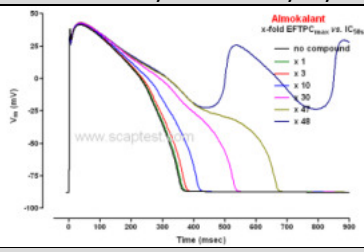
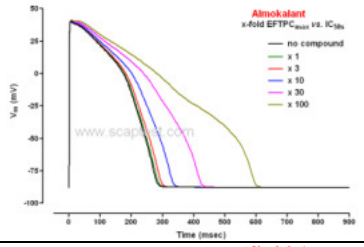
Human epicardial myocytes



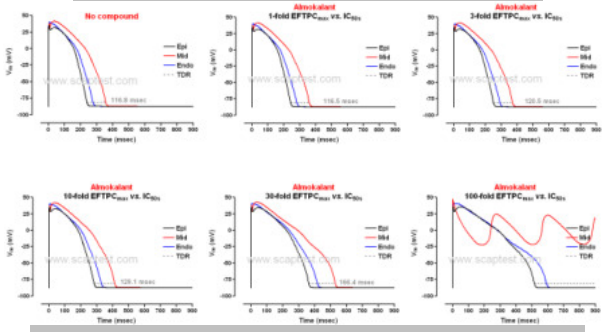
Human midmyocardial myocytes



Human endocardial myocytes

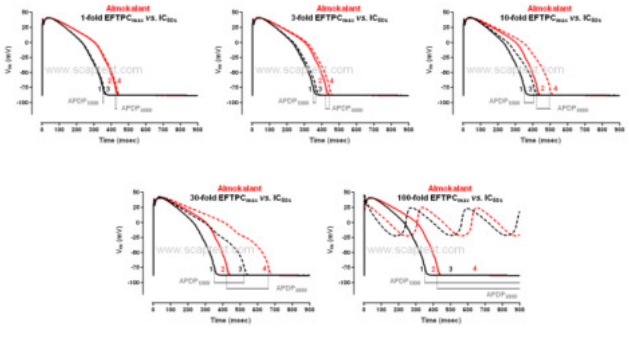


Transmural dispersion of repolarisation

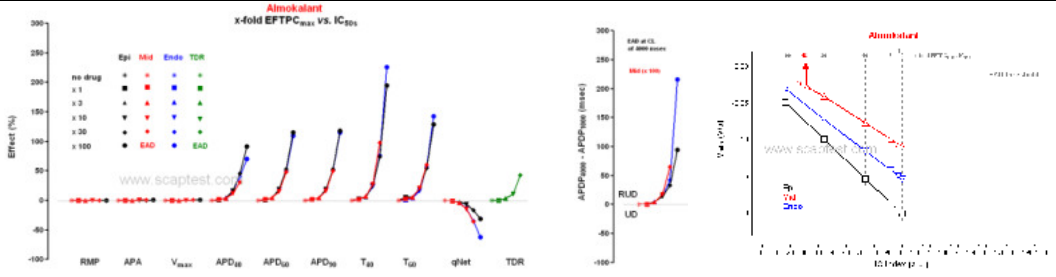


Reverse use dependence on midmyocardial myocytes

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
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4. Woosley RL (2015) www.CredibleMeds.org
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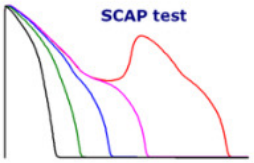
6. Wiśniowska B et al. (2017) *Drug discovery today* **22**: 10-16
7. O'Hara T et al. (2011) *PLoS Comput. Biol.* **7**: e1002061_8
8. Mirams GR et al. (2011) *Cardiovasc. Res.* **91**: 53-61
9. Christophe B & Crumb WJ Jr (2019) *J Pharmacol Toxicol Methods* **96**: 15-26

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 $I_{CaL}+I_{to}+I_{Na}+I_{to}+I_{NaL}+I_{K1}$, **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

Alvimopan

μ-opioid receptor antagonist used to avoid postoperative ileus

Raw data

IC_{50s} (slope) (1)

I_{CaL} : 5.012μM (1.0)
I_{to} : ---- μM (---)
I_{Kr} : 794.3 μM (1.0)
I_{NaL} : ---- μM (---)
I_{Na} : 251.2 μM (1.0)
I_{K1} : ---- μM (---)
I_{Ks} : 50.12 μM (1.0)

$EFTPC_{max}$ (1)

0.01049 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
- 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)
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TDR and RUD estimation:

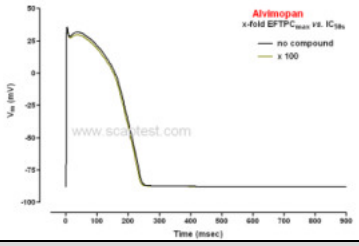
- TDR = APD_{90} mid - APD_{90} epi (at CL of 1000 msec)
- RUD = $APD_{90}P_{4000}$- $APD_{90}P_{1000}$

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

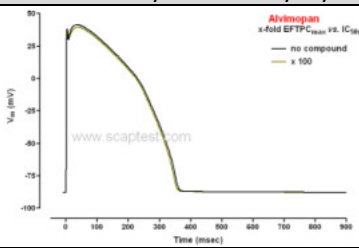
IC index calculation (9):

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

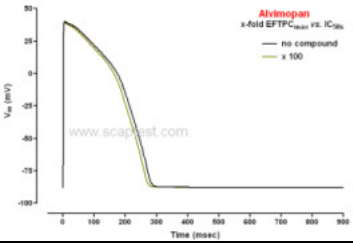
Human epicardial myocytes



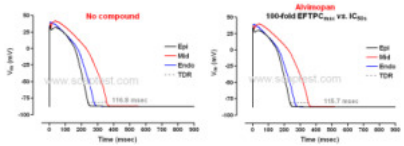
Human midmyocardial myocytes



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
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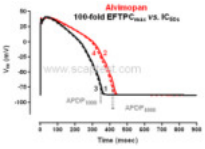
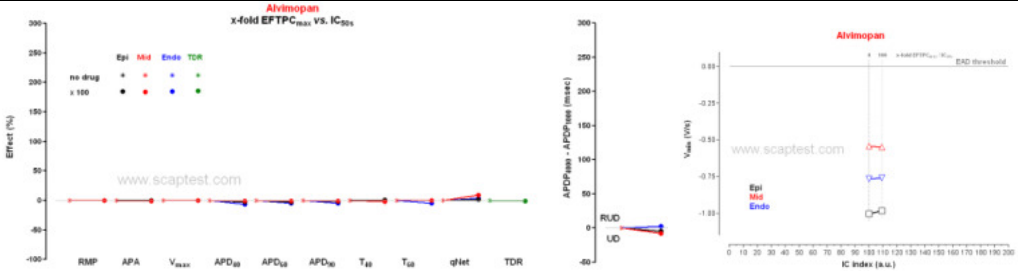
4 - CL 4000 msec with compound



Summary



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Abbreviations

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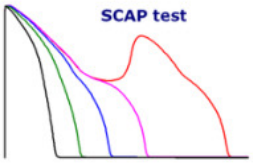

Drug

Ambrisentan

Endothelin ET_A antagonist used to treat pulmonary arterial hypertension

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 2511.9 µM (1.0)
I_{to} : 251.2 µM (1.0)
I_{Kr} : 501.2 µM (1.0)
I_{NaL} : ---- µM (---)
I_{Na} : 1258.9 µM (1.0)
I_{K1} : ---- µM (---)
I_{Ks} : 501.2 µM (1.0)

$EFTPC_{max}$ [1]

0.1676 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 = 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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IC50 = 50% of inhibition of a drug for channel 'j'
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where
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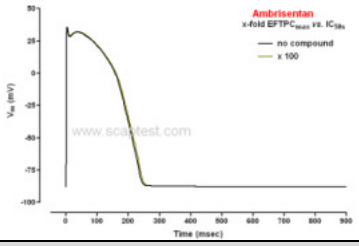
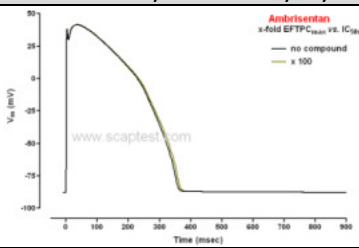
IC index calculation [9]:

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

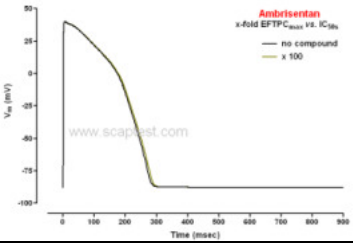
Human epicardial myocytes



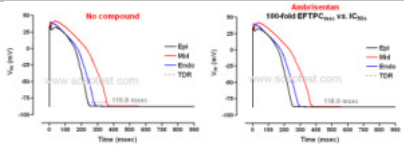
Human midmyocardial myocytes



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
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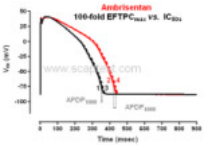
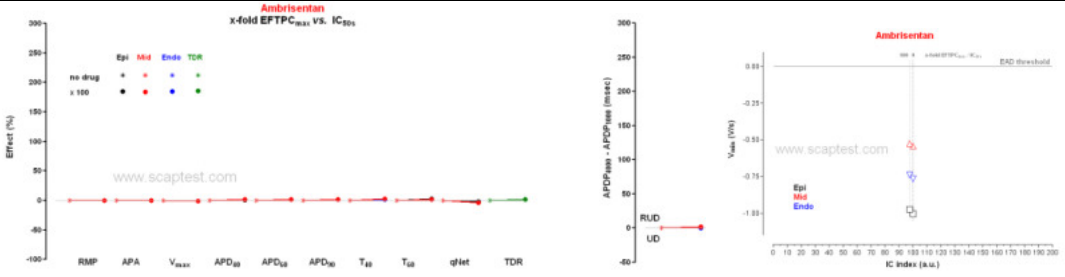


Summary



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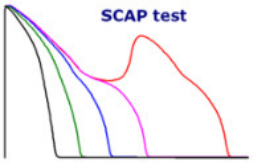


Drug

Amiodarone

Non-selective ionic channel blocker used as Class III antiarrhythmic to treat ventricular tachycardia

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 1.9 µM (0.69)
I_{Kr} : 0.86 µM (1.09)
I_{Na} : 15.9 µM (0.97)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ [1]

0.0008 µM

TdP risk

Redfern [2] : large but acceptable TdP risk (class 1)
Kramer [3] : torsadogenic (class 2)
CredibleMeds [4] : known risk of TdP (class 1)
CiPA [5] : not reported
WP [6] : 11/2 (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}

$$I_j = g\,O\,(V - E_{ion})$$

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:

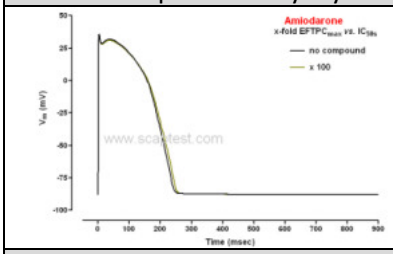
- TDR = APD_{90} mid - APD_{90} epi (at CL of 1000 msec)
- RUD = $APD_{90}P_{4000}$-$APD_{90}P_{1000}$

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

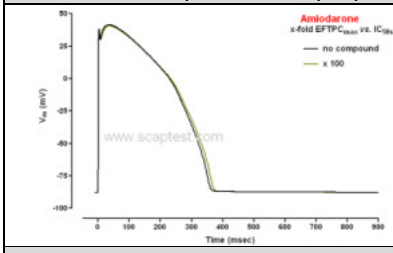
IC index calculation [9]:

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

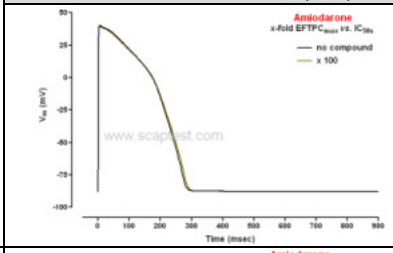
Human epicardial myocytes



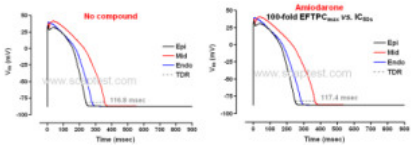
Human midmyocardial myocytes



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
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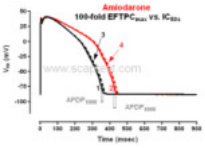
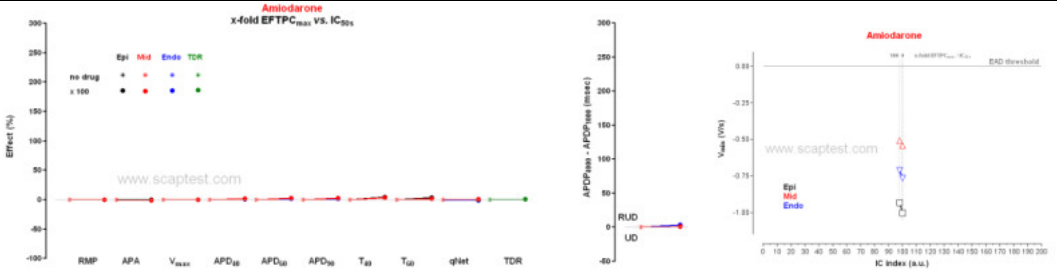


Summary



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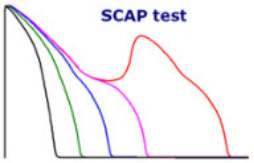
Abbreviations

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_{to}+I_{Na}+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

Amitriptyline

Serotonin and noradrenaline reuptake inihibitor used to treat depressive illness

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 1.291 µM (1.0)
I_{to} : 2.543 µM (0.4)
I_{Kr} : 3.660 µM (1.0)
I_{NaL} : 4.433 µM (0.5)
I_{Na} : 5.760 µM (1.3)
I_{K1} : ---- µM (---)
I_{Ks} : 2.737 µM (0.5)

$EFTPC_{max}$ [1]

0.0364 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] : 5/3 (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)

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

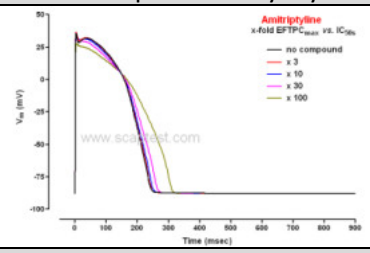
TDR and RUD estimation:

- 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

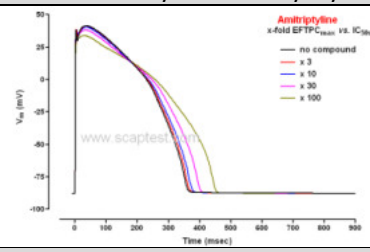
IC index calculation [9]:

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

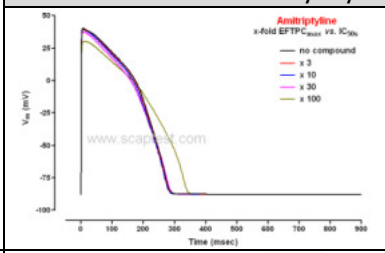
Human epicardial myocytes



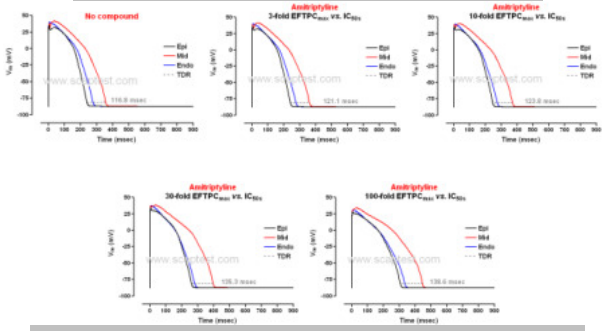
Human midmyocardial myocytes



Human endocardial myocytes

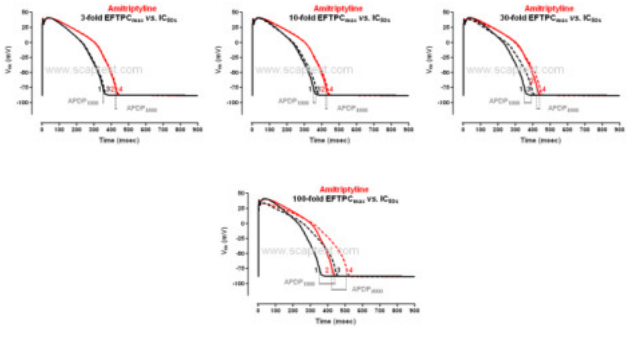


Transmural dispersion of repolarisation

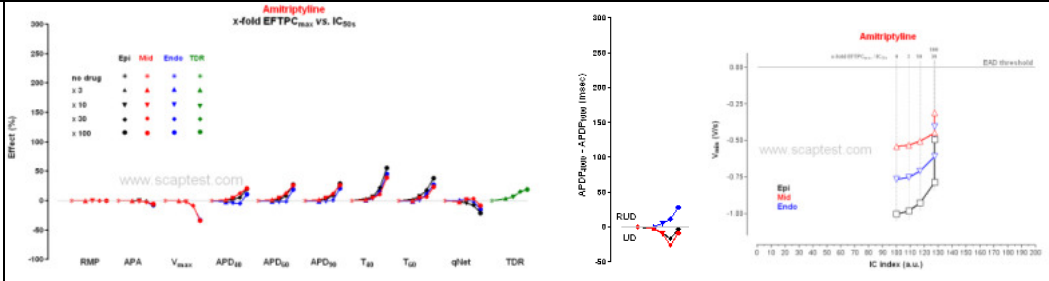


Reverse use dependence on midmyocardial myocytes

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.jisiextra.org/hesi/science/cardiac/cipa/Project
6. Wiśniowska B et al. (2017) *Drug discovery today* **22** : 10-16
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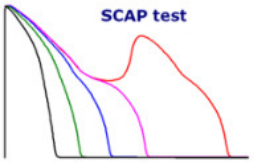

Drug

Amlodipine

L-type Ca^{++} channel ($Ca_V1.2$) blocker used to treat hypertension or angina

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 0.315µM (1.00)
I_{Kr} : 2.600 µM (1.33)
I_{Na} : 5.942 µM (1.00)
I_{Ks} : 5.900µM (1.65)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ [1]

0.105 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] : 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
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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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IC index calculation [9]:

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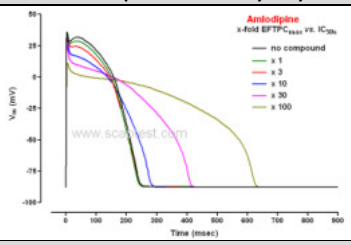
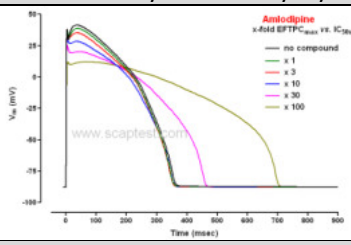
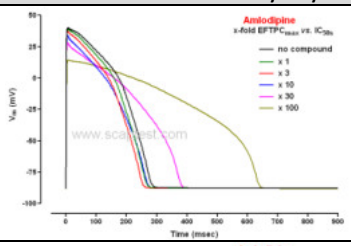
Human epicardial myocytes



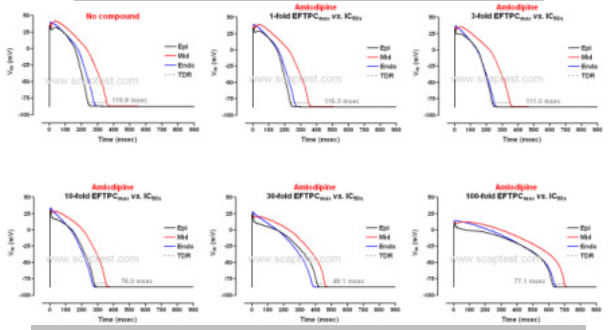
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarisation



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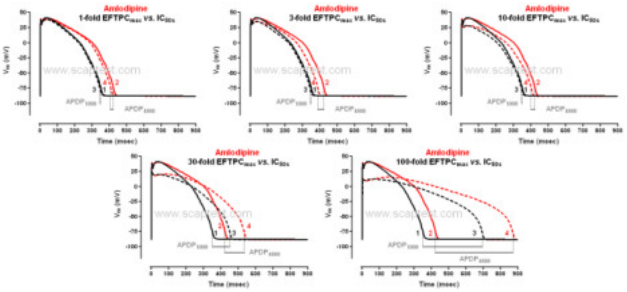

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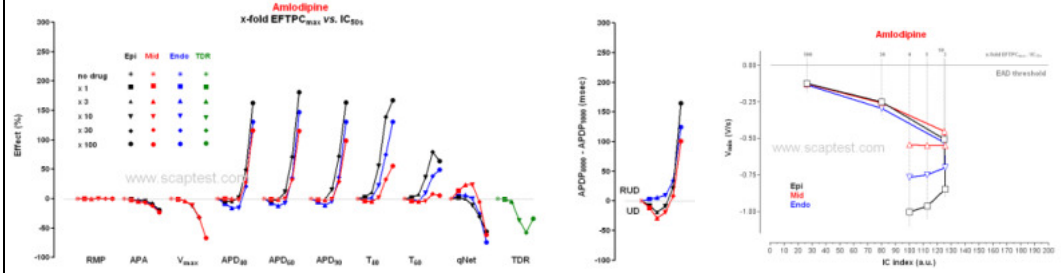

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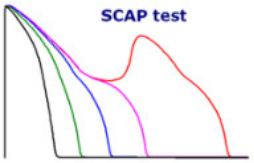

Drug

Aspirin

Cyclooxygenase COX-1 and COX-2 inhibitor used to treat pain, fever, inflammation, migraine, or to prevent adverse cardiovascular events
no longer marketed in UK, US, Hong Kong, Nigeria and Spain (Onakpoya et al (2016) *BMC Med.* **14**: 10)

Raw data

IC_{50s} (slope) [1]

I_{CaL} : ---- µM (---)
I_{to} : ---- µM (---)
I_{Kr} : 100000 µM (1.0)
I_{NaL} : ---- µM (---)
I_{Na} : ---- µM (---)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ [1]

7.7 µM

TdP risk

Redfern [2] : not reported
Kramer [3] : not reported
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CiPA [5] : not reported
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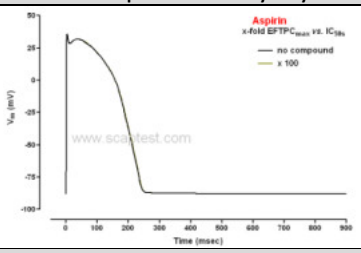
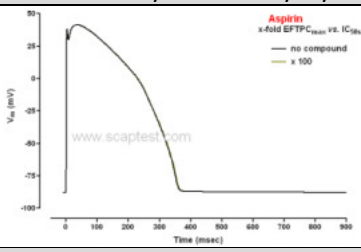
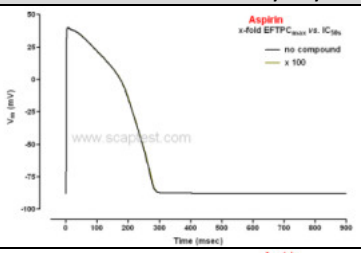
Human epicardial myocytes



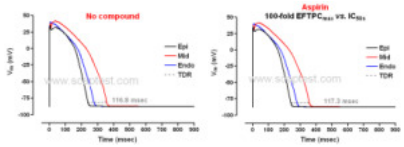
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarisation



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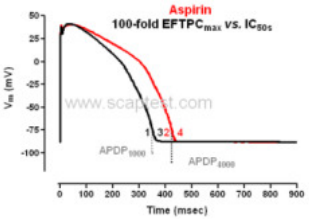

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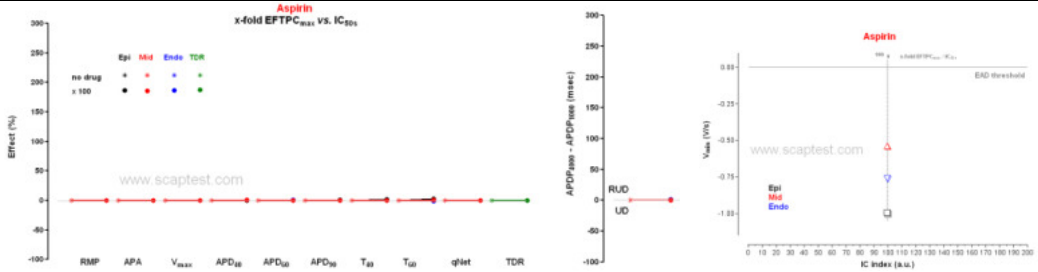

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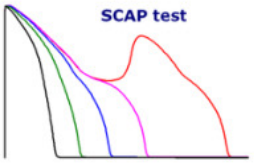

Drug

Astemizole

Histamine H_1-receptor antagonist used to treat allergy symptoms
no longer marketed worldwide (Onakpoya et al (2016) *BMC Med.* **14**: 10)

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 1.1 µM (1.66)
I_{Kr} : 0.004 µM (0.78)
I_{Na} : 3.0 µM (1.95)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ [1]

0.0003 µM

TdP risk

Redfern [2] : unacceptable risk of TdP (class 2)
Kramer [3] : torsadogenic (class 2)
CredibleMeds [4] : known risk of TdP (class 1)
CiPA [5] : intermediate risk (class 2)
WP [6] : 14/0 (TdP+/TdP-)

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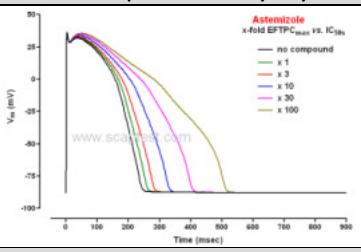
D= drug concentration (EFTPC for example)
n= hill slope

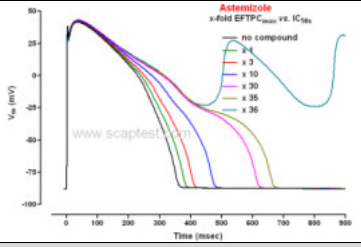
TDR and RUD estimation:
- TDR = APD_{90} mid - APD_{90} epi (at CL of 1000 msec)
- RUD = $APD_{90}P_{1000}$-$APD_{90}P_{1000}$
where
$APD_{90}P_x$ = APD_{90} with - APD_{90} without compound at CL x

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}

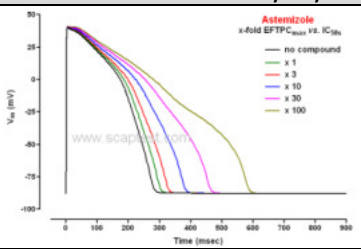
Human epicardial myocytes



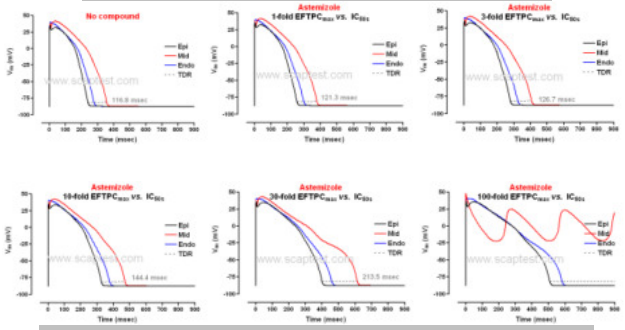
Human midmyocardial myocytes



Human endocardial myocytes

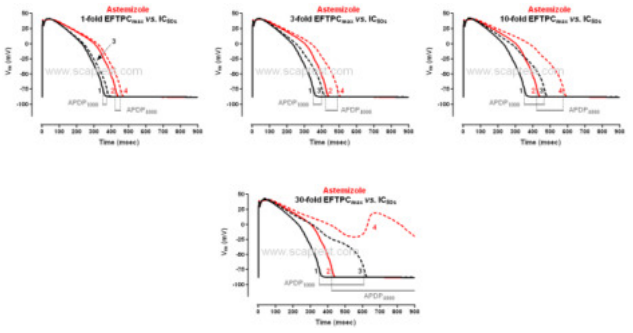


Transmural dispersion of repolarisation

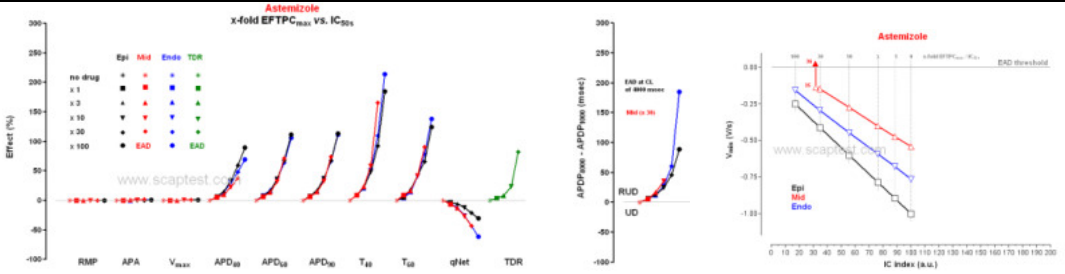


Reverse use dependence on midmyocardial myocytes

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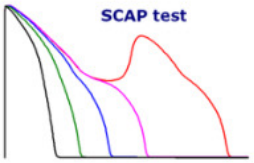
8. Mirams GR et al. (2011) *Cardiovasc. Res.* **91** : 53-61
9. Christophe B & Crumb WJ Jr (2019) *J Pharmacol Toxicol Methods* **96** : 15-26

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 $I_{CaL}+I_{Kr}+I_{Ks}+I_{to}+I_{NaL}+I_{K1}$, **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

Atenolol

β_1-adrenenoceptor antagonist used to treat hypertension or chronic angina

Raw data

IC_{50s} (slope) [1]

I_{CaL} : ---- µM (---) I_{to} : ---- µM (---)
I_{Kr} : 1500 µM (0.92) I_{NaL} : ---- µM (---)
I_{Na} : ---- µM (---) I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ [1]

1.156 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] : 0/1 (TdP+/TdP-) 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'
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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
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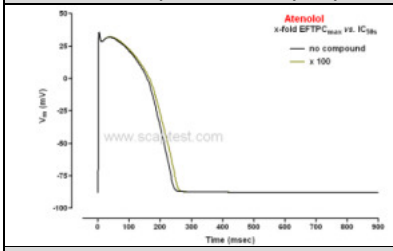
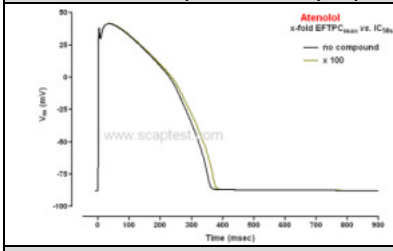
IC index calculation [9]:

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

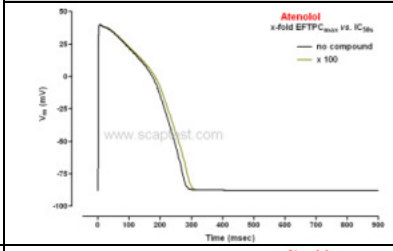
Human epicardial myocytes



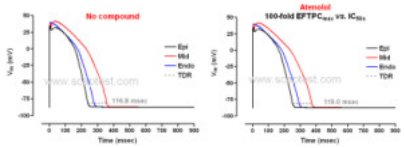
Human midmyocardial myocytes



Human endocardial myocytes

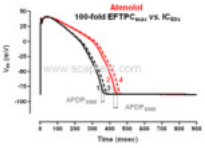


Transmural dispersion of repolarisation

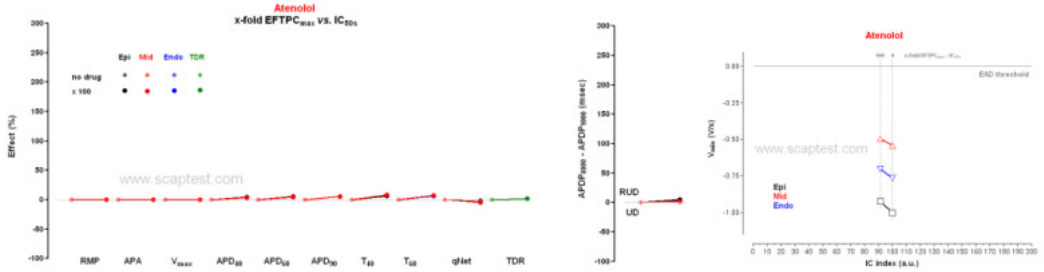


Reverse use dependence on midmyocardial myocytes

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

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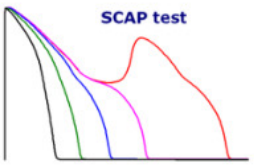

Drug

Azimilide

Slow and rapid delayed rectifier K^+ voltage-gated (K_V7.1 and K_V11.1) channel blocker under clinical trials as Class III anti-arrhythmic (in USA , Drugbank on line)

Raw data

IC_{50s} (slope) [1]

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 (---)

$EFTPC_{max}$ [1]

0.072 µM

TdP risk

Redfern [2] : large but acceptable TdP risk (class 1)
Kramer [3] : not reported
CredibleMeds [4] : not reported but under review
CiPA [5] : high risk (class 1)
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_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'
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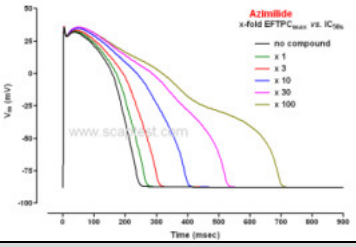
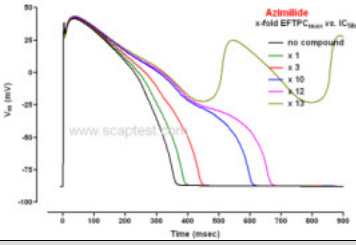
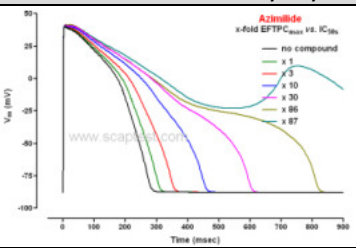
Human epicardial myocytes



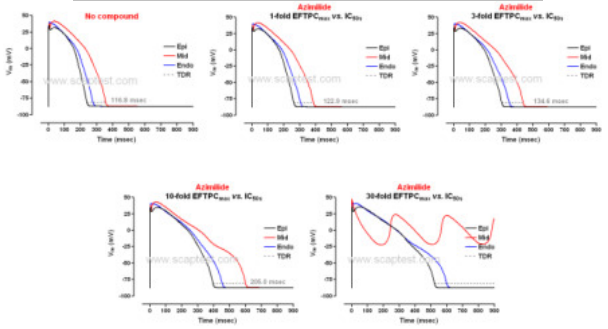
Human midmyocardial myocytes



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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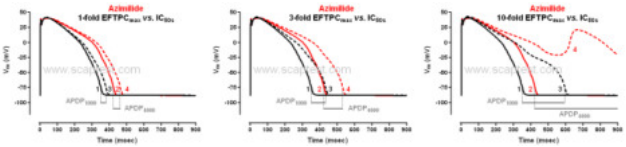
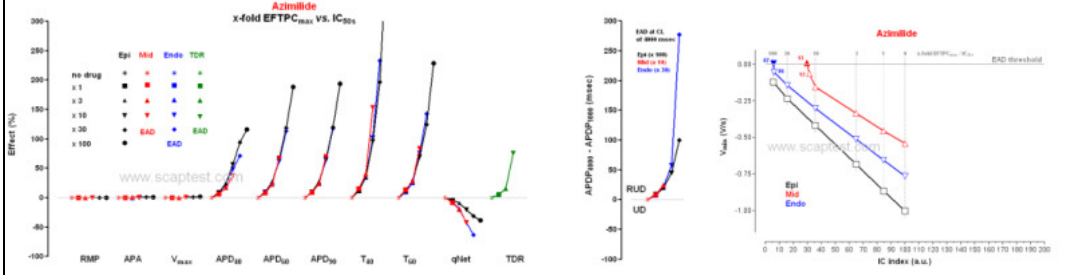


Summary



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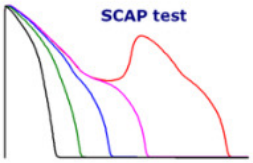

Drug

Azithromycin

Macrolide antibiotic used to treat a variety of bacterial infections

Raw data

IC_{50s} (slope) [1]

I_{CaL} : ---- µM (---)
I_{to} : 88.764 µM (0.5)
I_{Kr} : 70.796 µM (0.5)
I_{NaL} : 189.128 µM (1.9)
I_{Na} : ---- µM (---)
I_{K1} : ---- µM (---)
I_{Ks} : 470.131 µM (1.4)

$EFTPC_{max}$ [1]

1.937 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] : 5/1 (TdP+/TdP-)

Results

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

Simulation conditions:

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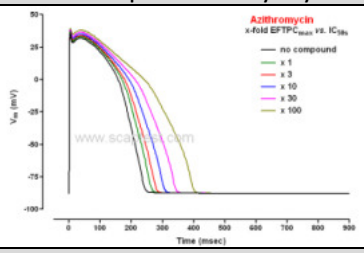
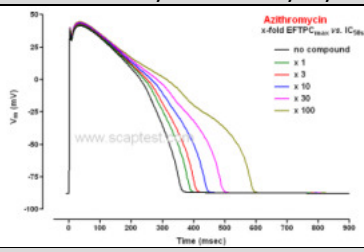
where
AFKr, AFNaL and AFCaL = active fraction (%) of the I_{Kr}, I_{NaL} and I_{CaL}

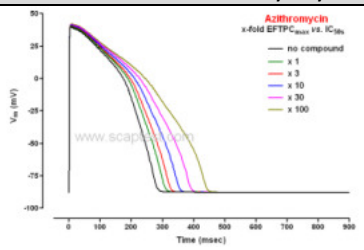
Human epicardial myocytes



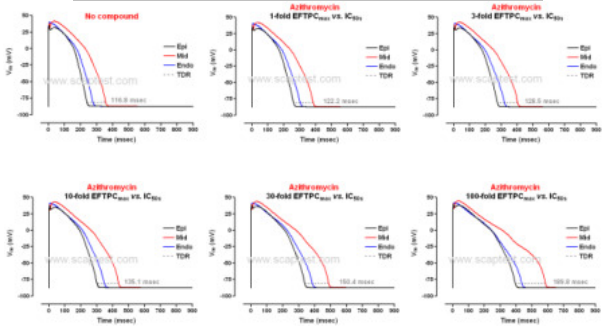
Human midmyocardial myocytes



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
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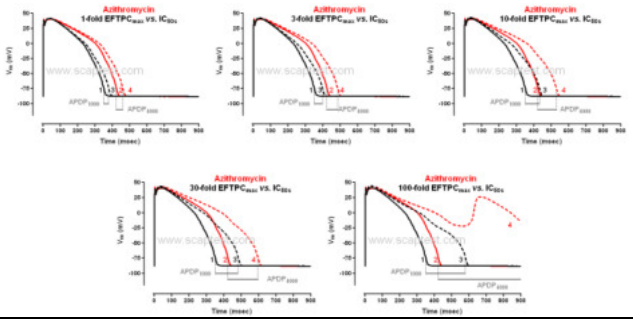
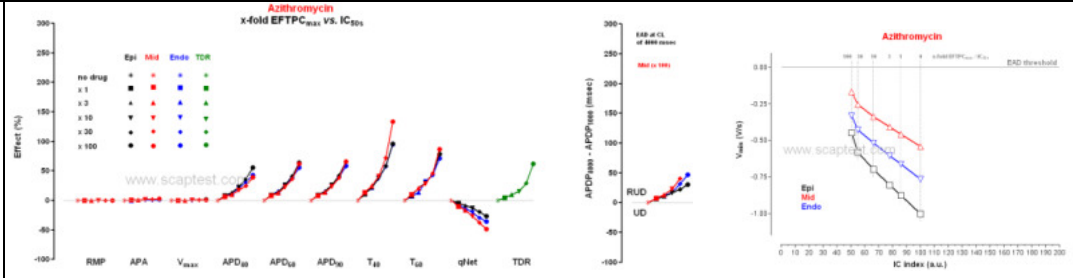


Summary



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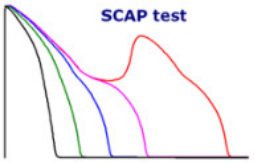
2. Redfern WS et al. (2003) *Cardiovasc. Res.* **58** : 32-45
3. Kramer J et al. (2013) *Sci.rep.* **3** : 2100
4. Woosley RL (2015) www.CredibleMeds.org
5. CiPA (2016) www.ilsiextra.org/hesi/science/cardiac/cipa/Project
6. Wiśniowska B et al. (2017) *Drug discovery today* **22** : 10-16
7. O'Hara T 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

Bepridil

L-type Ca^{++} channel ($Ca_V1.2$) blocker used to treat angina and hypertension
no longer marketed in USA (Onakpoya et al (2016) *BMC Med.* **14**: 10)

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 1.00 µM (1.28)
I_{Kr} : 0.16 µM (0.88)
I_{Na} : 2.30 µM (1.26)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ [1]

0.035 µM

TdP risk

Redfern [2] : numerous reports of TdP (class 3)
Kramer [3] : torsadogenic (class 2)
CredibleMeds [4] : known risk of TdP (class 1)
CiPA [5] : High risk (class 1)
WP [6] : 15/0 (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'

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

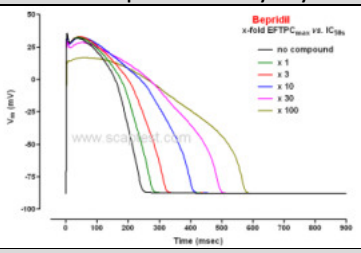
g_j = maximal conductance of channel 'j'
$g_{control,j}$ = drug-free maximal conductance of channel 'j'
IC50 = 50% of inhibition of a drug for channel 'j'
D= drug concentration (EFTPC for example)
n= hill slope

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

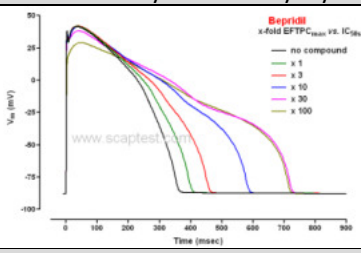
where
$APD_{90}P_x$ = APD_{90} with - APD_{90} without compound at CL x

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}.

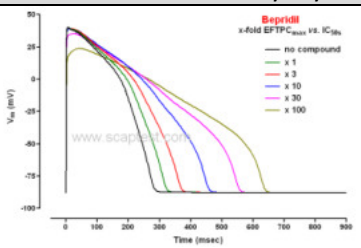
Human epicardial myocytes



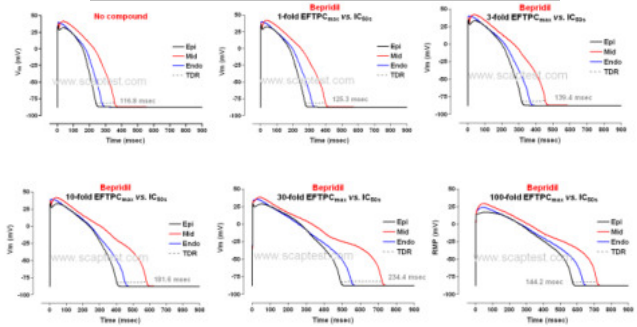
Human midmyocardial myocytes



Human endocardial myocytes

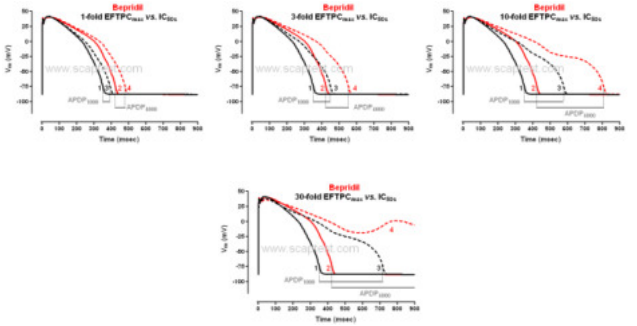


Transmural dispersion of repolarisation

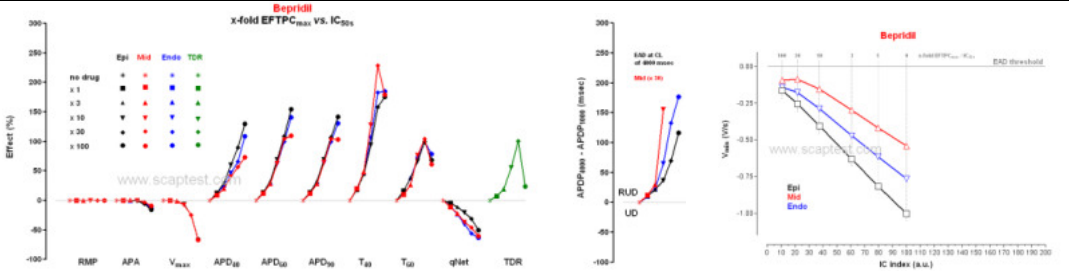


Reverse use dependence on midmyocardial myocytes

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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2. Redfern WS et al. (2003) *Cardiovasc. Res.* **58** : 32-45
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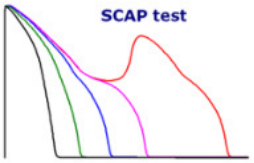
Abbreviations

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_{to}+I_{Na}+I_{NaL}+I_{Kr}, **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	**Ceftriaxone** Cephalosporin antibiotic used to treat various gram-negative bacterial infections

Raw data

IC_{50s} (slope) [1]		$EFTPC_{max}$ [1]	TdP risk
I_{CaL} : 153.8µM (1.0)	I_{to} : ---- µM (---)	23.17 µM	Redfern [2] : not reported
I_{Kr} : 445.7 µM (1.0)	I_{NaL} : ---- µM (---)		Kramer [3] : non-torsadogenic (class 1)
I_{Na} : 555.9 µM (1.0)	I_{K1} : ---- µM (---)		CredibleMeds [4] : not classified with TdP risk (class 4)
I_{Ks} : ---- µM (---)			CiPA [5] : not reported
			WP [6] : 0/3 (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}

$$I_j = g\,O(V - E_{ion})$$

g = maximal conductance of channel 'j'
O=open probability of channel 'j'
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where
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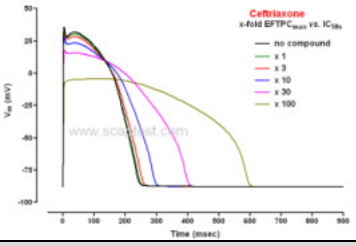
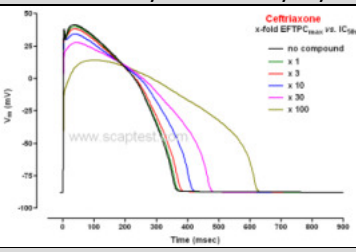
IC index calculation [9]:
IC index = (AFKr/((AFNaL+AFCaL)/2))*100
where
AFKr, AFNaL and AFCaL = active fraction (%) of the I_{Ks}, I_{NaL} and I_{CaL}.

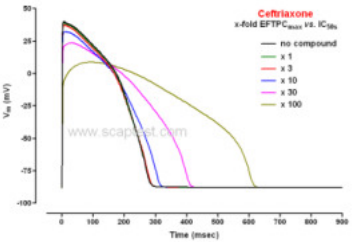
Human epicardial myocytes



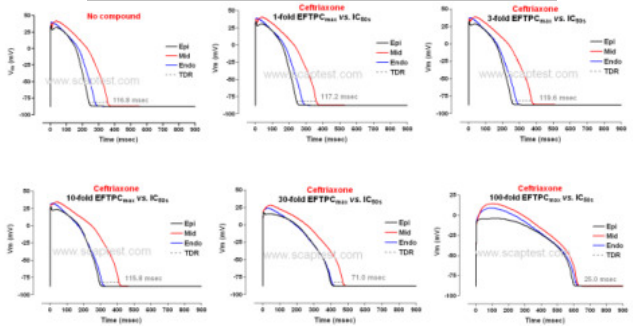
Human midmyocardial myocytes



Human endocardial myocytes

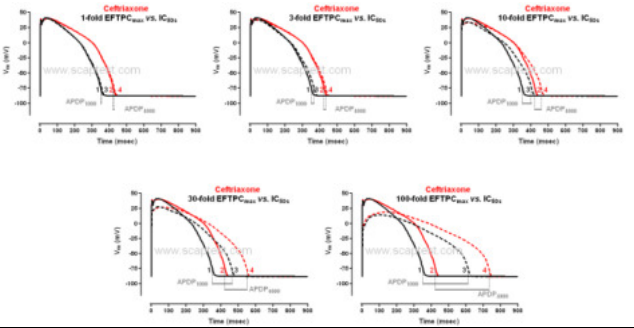


Transmural dispersion of repolarisation

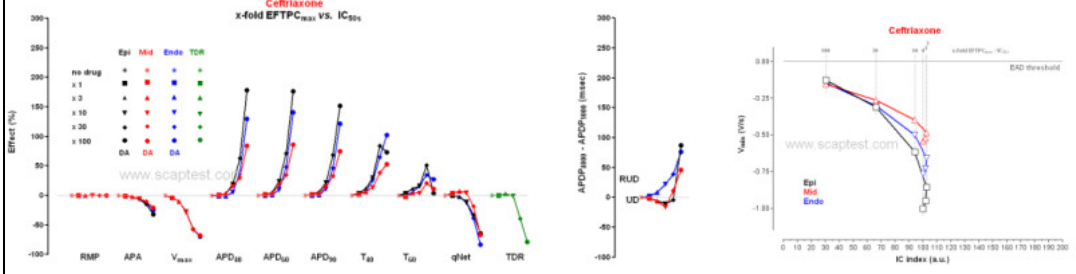


Reverse use dependence on midmyocardial myocytes

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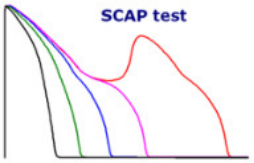

Drug

Cetirizine

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

Raw data

IC_{50s} (slope) [1]

I_{CaL} : ---- µM (---)
I_{to} : ---- µM (---)
I_{Kr} : 240.0 µM (1.0)
I_{NaL} : ---- µM (---)
I_{Na} : ---- µM (---)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ [1]

0.056 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] : 0/3 (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)

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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

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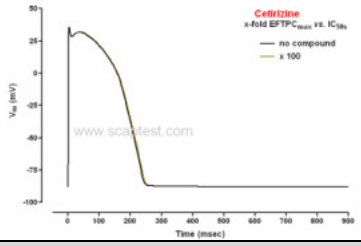
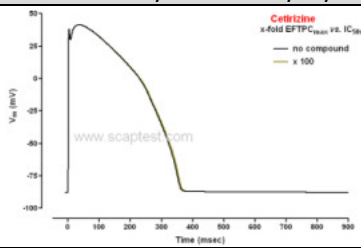
IC index = (AFKr/((AFNaL+AFCaL)/2))*100
where
AFKr, AFNaL and AFCaL = active fraction (%) of the I_{Ks}, I_{NaL} and I_{CaL}.

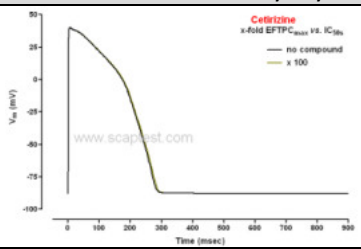
Human epicardial myocytes



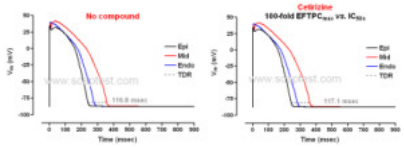
Human midmyocardial myocytes



Human endocardial myocytes

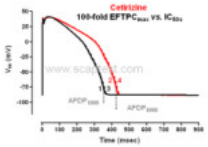


Transmural dispersion of repolarisation

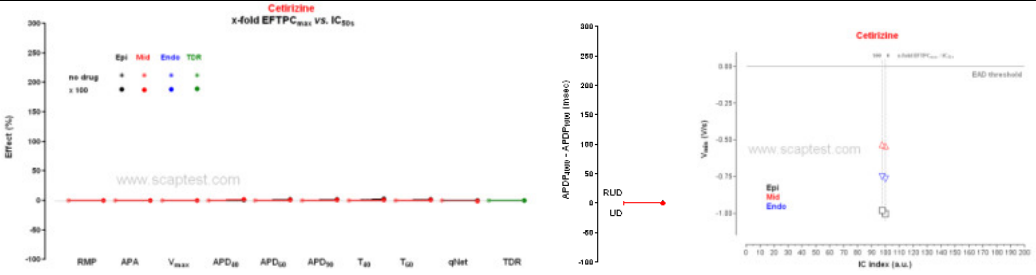


Reverse use dependence on midmyocardial myocytes

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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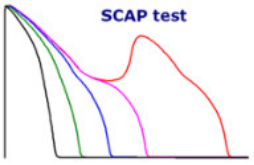

Drug

Chloroquine

Ferriprotophorphyrin IX complexing agent used to treat malaria
no longer marked in Japan (Onakpoya et al (2016) *BMC Med.* **14**: 10)

Raw data

IC_{50s} (slope) [1]

I_{CaL} : ---- µM (---)
I_{Kr} : 6.889 µM (0.6)
I_{Na} : ---- µM (---)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : 10.595 µM (0.8)

$EFTPC_{max}$ [1]

0.2495 µM

TdP risk

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

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:

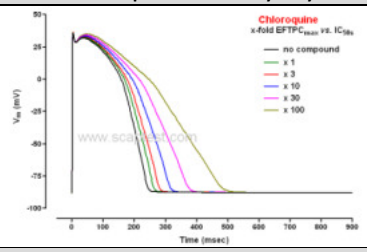
- TDR = APD_{90} mid - APD_{90} epi (at CL of 1000 msec)
- RUD = $APD_{90}P_{x000}$-$APD_{90}P_{1000}$

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

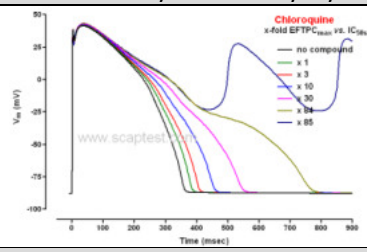
IC index calculation [9]:

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

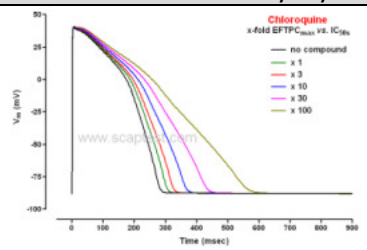
Human epicardial myocytes



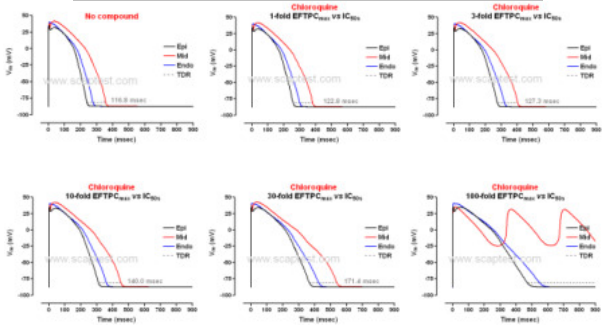
Human midmyocardial myocytes



Human endocardial myocytes

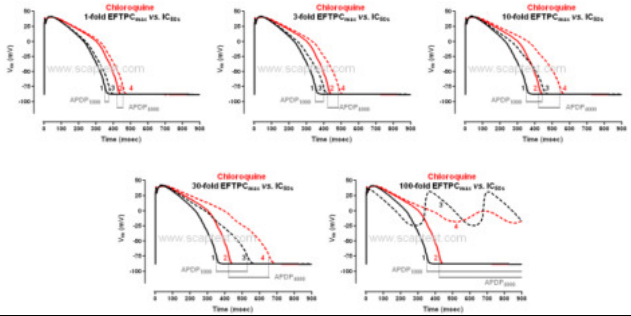


Transmural dispersion of repolarisation

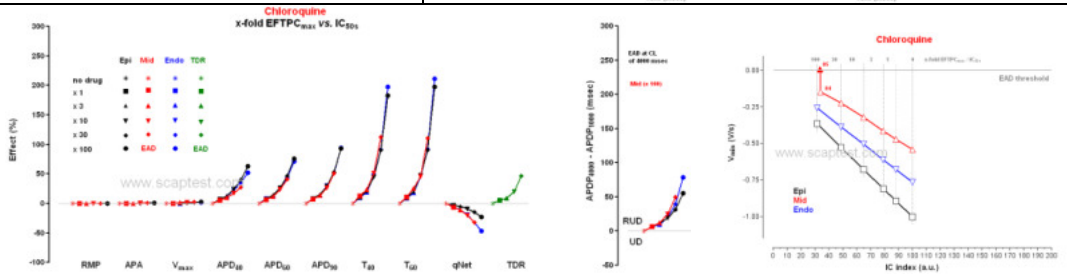


Reverse use dependence on midmyocardial myocytes

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
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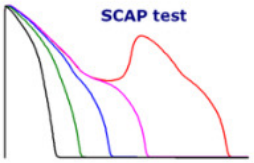
6. Wiśniowska B et al. (2017) *Drug discovery today* **22 :** 10-16
7. O'Hara T et al. (2011) *PLoS Comput. Biol.* **7 :** e1002061,8
8. Mirams GR et al. (2011) *Cardiovasc. Res.* **91 :** 53-61
9. Christophe B & Crumb WJ Jr (2019) *J Pharmacol Toxicol Methods* **96 :** 15-26

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_{to}+I_{Na}+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

Chlorpheniramine

Histamine H_1-receptor antagonist used to treat upper respiratory allergies

Raw data

IC_{50s} (slope) [1]

I_{CaL} : ---- µM (---)
I_{to} : ---- µM (---)
I_{Kr} : 13.00 µM (1.00)
I_{NaL} : ---- µM (---)
I_{Na} : ---- µM (---)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ [1]

0.012 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] : 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}

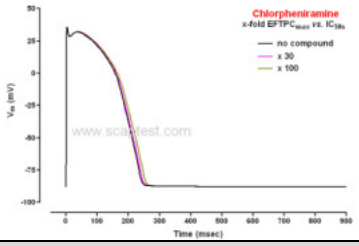
$I_j = g_j O(V - E_{ion})$

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

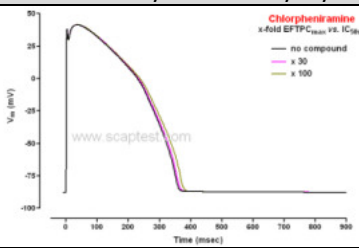
TDR and RUD estimation:
- TDR = APD_{90} mid - APD_{90} epi (at CL of 1000 msec)
- RUD = $APD_{90}P_{x400}$- $APD_{90}P_{1000}$ where $APD_{90}P_x$ = APD_{90} with - APD_{90} without compound at CL x

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}.

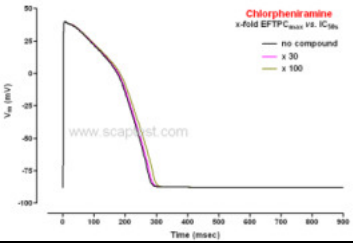
Human epicardial myocytes



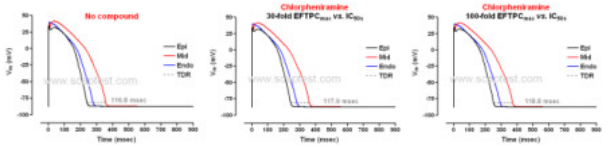
Human midmyocardial myocytes



Human endocardial myocytes

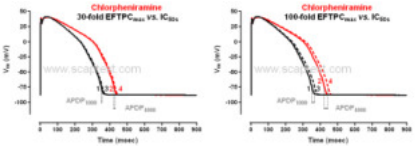


Transmural dispersion of repolarisation

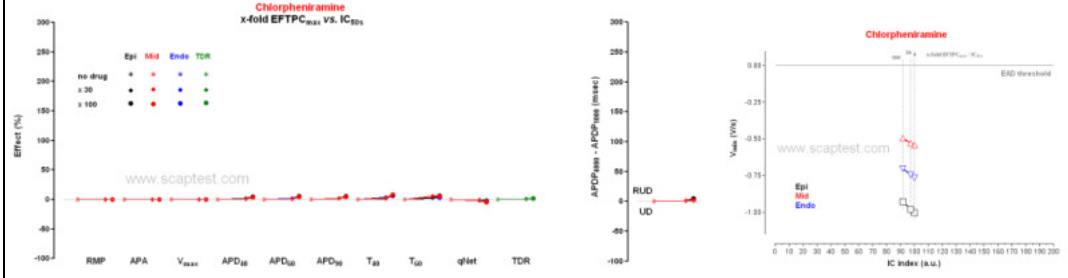


Reverse use dependence on midmyocardial myocytes

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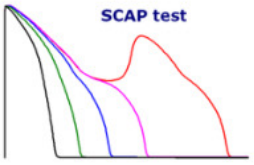
Abbreviations

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_{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_{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

Chlorpromazine

Non selective dopamine and setotonin receptor antagonist used to treat nausea, vomiting, anxiety, schizophrenia and bipolar disorder

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 3.4 µM (1.73)
I_{Kr} : 1.5 µM (1.4)
I_{Na} : 3.0 µM (1.14)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ [1]

0.038 µM

TdP risk

Redfern [2] : numerous TdP reports (class 3)
Kramer [3] : torsadogenic drig (class 2)
CredibleMeds [4] : known risk of TdP (class 1)
CiPA [5] : intermediate risk (class 2)
WP [6] : 11/0 (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_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= fold slope

TDR and RUD estimation:

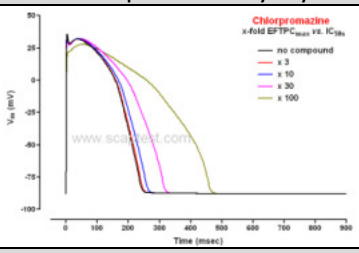
- TDR = APD_{90} mid - APD_{90} epi (at CL of 1000 msec)
- RUD = $APD_{90}P_{4000}$- $APD_{90}P_{1000}$

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

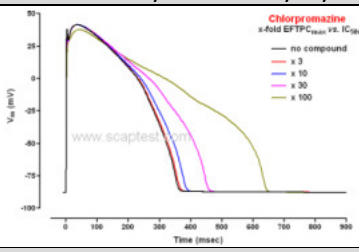
IC index calculation [9]:

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

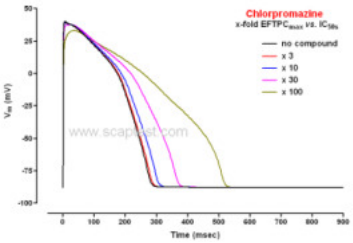
Human epicardial myocytes



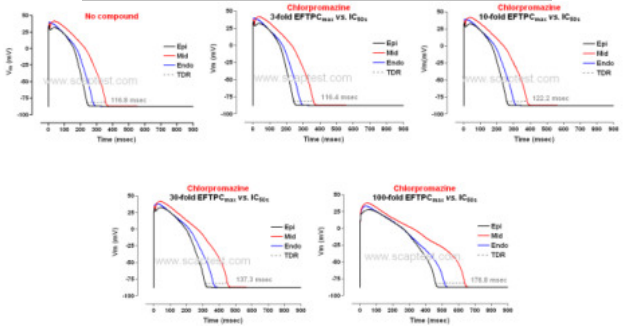
Human midmyocardial myocytes



Human endocardial myocytes

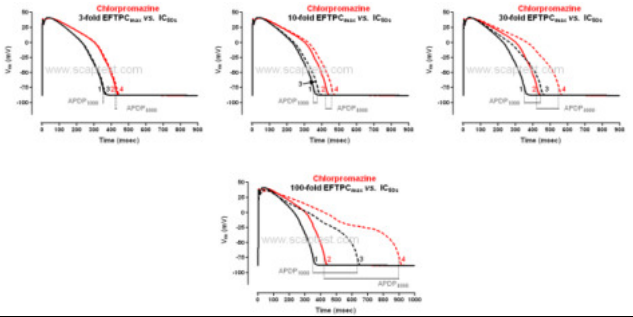


Transmural dispersion of repolarisation

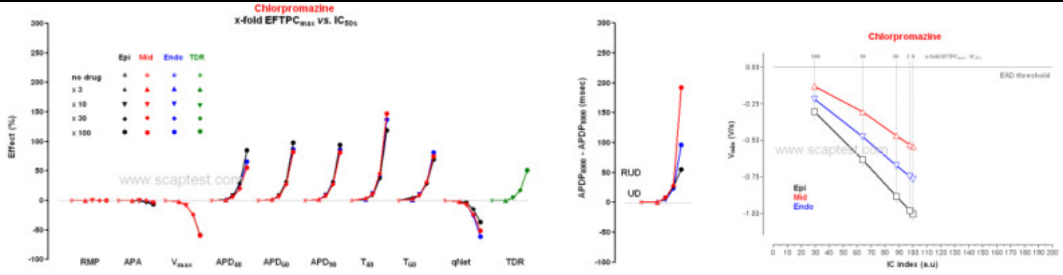


Reverse use dependence on midmyocardial myocytes

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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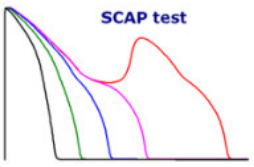

Drug

Cibenzoline

K_{ATP} channel (Kir 6.2) blocker used as Class IC antiarrhythmic to treat arrhythmia

Raw data

IC_{50s} (slope) [1]

I_{CaL} : ---- µM (---)
I_{to} : ---- µM (---)
I_{Kr} : 2.097 µM (0.9)
I_{NaL} : 46.581 µM (0.6)
I_{Na} : 21.752 µM (1.2)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ [1]

0.673 µM

TdP risk

Redfern [2] : no published report of TdP (Class 5)
Kramer [3] : not reported
CredibleMeds [4] : not reported
CiPA [5] : not reported
WP [6] : 0/4 (TdP+/TdP-)

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

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- 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}

$$I_j = g\,O\,(V - E_{ion})$$

g = maximal conductance of channel 'j'
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E_{ion}= reversal potential for species of ions which flows through channel 'j'

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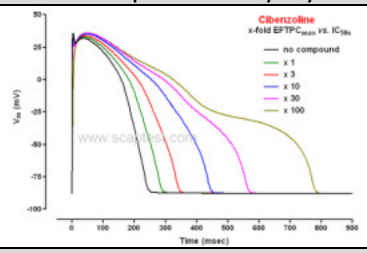
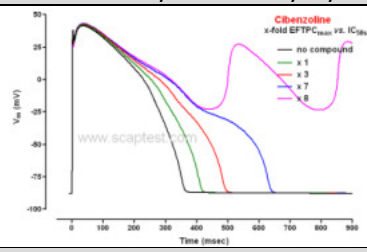
where
AFKr, AFNaL and AFCaL = active fraction (%) of the I_{Kr}, I_{NaL} and I_{CaL}

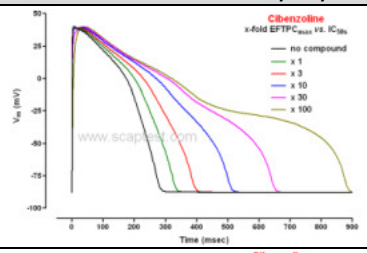
Human epicardial myocytes



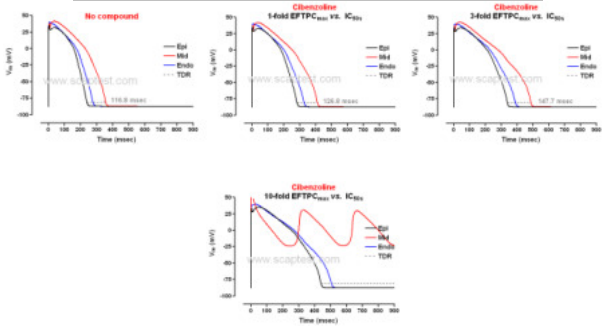
Human midmyocardial myocytes



Human endocardial myocytes

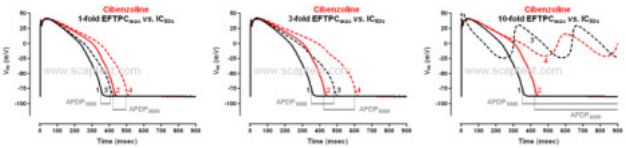


Transmural dispersion of repolarisation

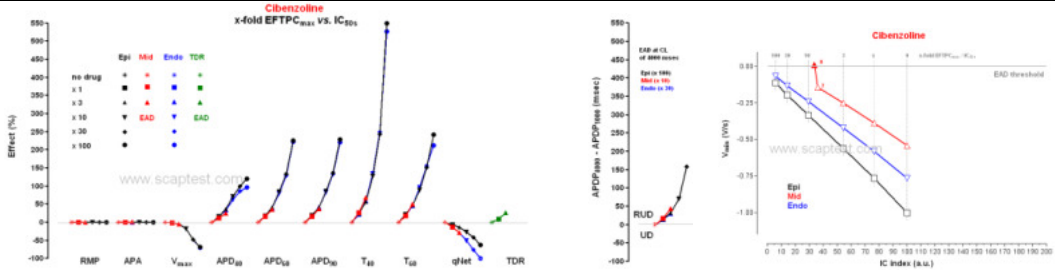


Reverse use dependence on midmyocardial myocytes

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



Summary

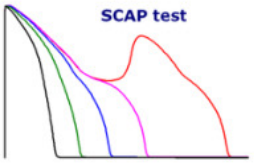


References

1. Crumb WJ et al. (2016) *J Pharmacol Toxicol Methods* **81 :** 251-262
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_{to}+I_{Na}+I_{NaL}+I_{Kr}, **RMP** : resting membrane potential, **RUD** : reverse use dependence, **$T_{40,60}$** : APD_{90}-APD_{40} or APD_{60} (°triangulation), **TdP** : torsade de pointes , **TDR** : transmural dispersion of repolarization, **V_m** : membrane voltage, **V_{max}** : maximal rate of AP rise , **V_{min}** : minimal rate of AP decrease at EAD take-off voltage, **V/s** : volt per second



Drug

Cilostazol

cAMP phosphodiesterase III (PDE_{3A}) inhibitor used as antiplatelet agent and vasodilator to treat intermittent claudication

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 91.2 µM (1.0)
I_{Kr} : 13.8 µM (0.91)
I_{Na} : 93.7 µM (1.0)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ [1]

0.128 µM

TdP risk

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

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

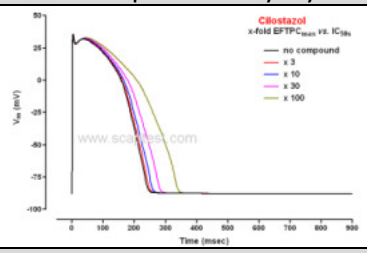
g = maximal conductance of channel 'j'
$g_{control,j}$ = drug free maximal conductance of channel 'j'
IC50 = 50% of inhibition of a drug for channel 'j'
D= drug concentration (EFTPC for example)
n= hill slope

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

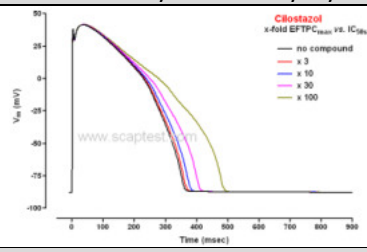
where
$APD_{90}P_x$ = APD_{90} with - APD_{90} without compound at CL x

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}.

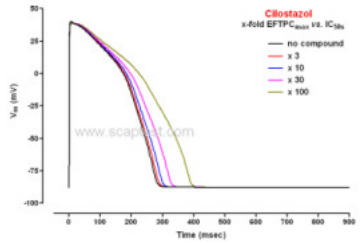
Human epicardial myocytes



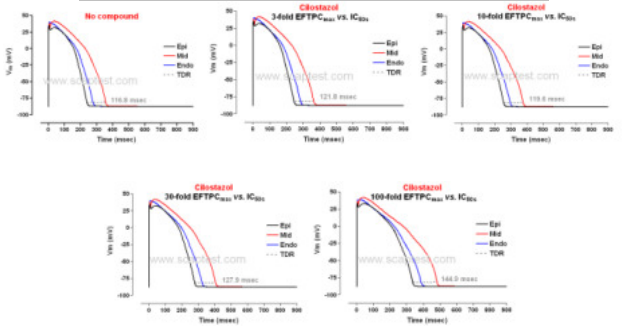
Human midmyocardial myocytes



Human endocardial myocytes

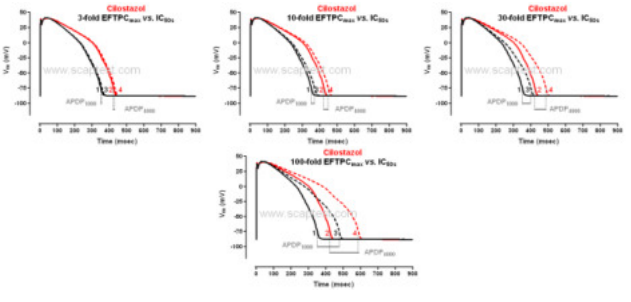


Transmural dispersion of repolarisation

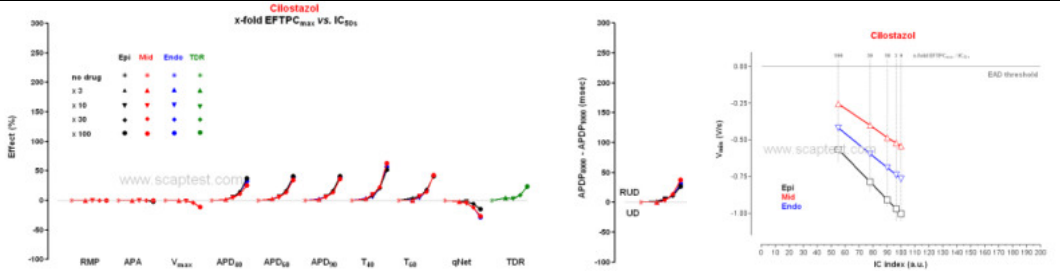


Reverse use dependence on midmyocardial myocytes

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

Abbreviations

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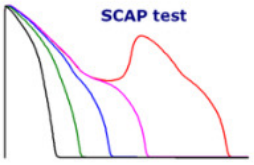

Drug

Ciprofloxacin

Fluoroquinolone antibiotic used to treat various bacterial infections

Raw data

IC_{50s} (slope) [1]

I_{CaL} : ---- µM (---) I_{to} : ---- µM (---)
I_{Kr} : 335.0 µM (1.00) I_{NaL} : ---- µM (---)
I_{Na} : ---- µM (---) I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ [1]

12.072 µM

TdP risk

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

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

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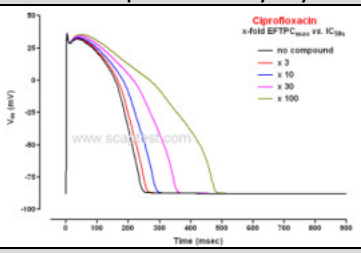
TDR and RUD estimation:
- TDR = APD_{90} mid - APD_{90} epi (at CL of 1000 msec)
- RUD = $APD_{90}P_{4000}$- $APD_{90}P_{1000}$

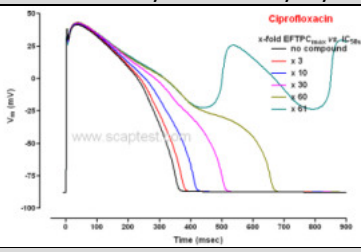
where
$APD_{90}P_x$ = APD_{90} with - APD_{90} without compound at CL x

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}.

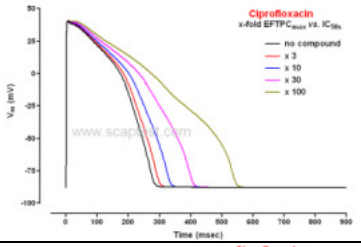
Human epicardial myocytes



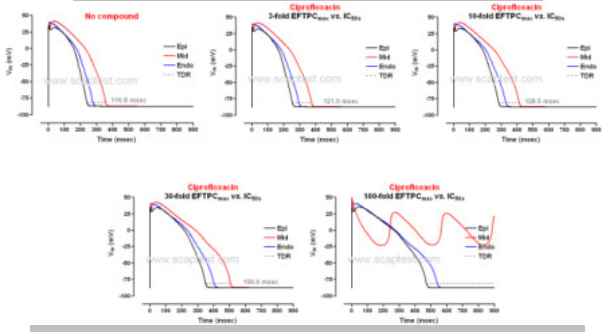
Human midmyocardial myocytes



Human endocardial myocytes

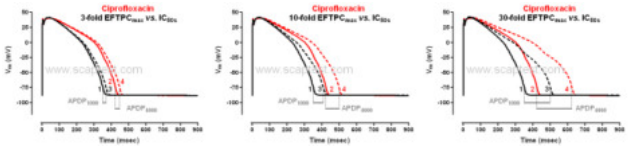


Transmural dispersion of repolarisation

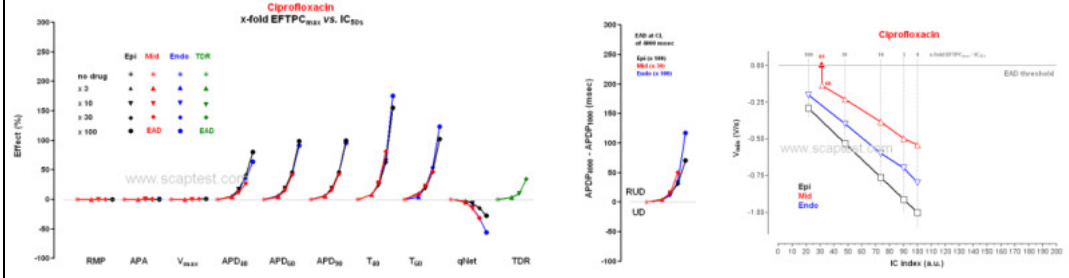


Reverse use dependence on midmyocardial myocytes

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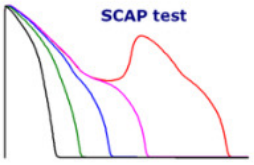

Drug

Cisapride

Serotonin 5-HT$_4$ agonist used to treat gastroesophageal reflux disease
no longer marketed worldwide (Onakpoya et al (2016) *BMC Med.* **14**: 10)

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 11.8 µM (1.0)
I_{Kr} : 0.02 µM (1.04)
I_{Na} : 337.0 µM (1.0)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ [1]

0.003 µM

TdP risk

Redfern [2] : unacceptable risk of TdP (class 2)
Kramer [3] : torsadogenic (class 2)
CredibleMeds [4] : known risk of TdP (class 1)
CiPA [5] : intermediate risk of TdP (class 2)
WP [6] : 16/0 (TdP+/TdP-)

Results

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

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

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

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

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

TDR and RUD estimation:
- TDR = APD_{95} mid - APD_{95} epi (at CL of 1000 msec)
- RUD = $APD_{90}P_{x000}$-$APD_{90}P_{1000}$

where
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IC index calculation [9]:
IC index = (AFKr/((AFNaL+AFCaL)/2))*100
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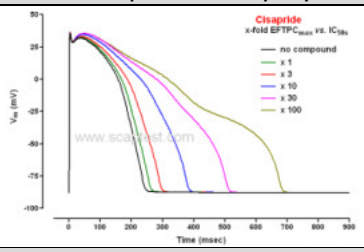
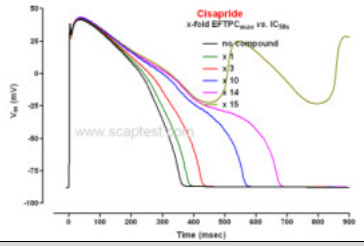
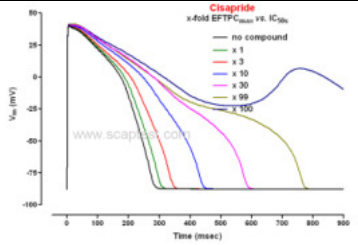
Human epicardial myocytes



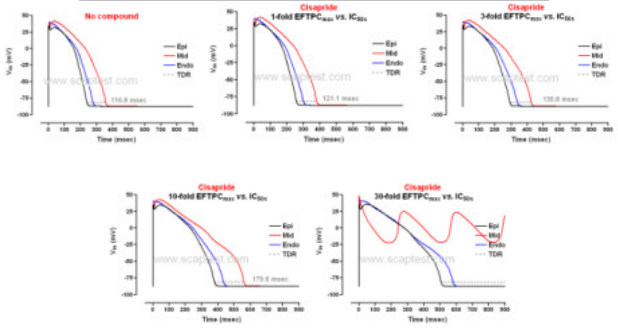
Human midmyocardial myocytes



Human endocardial myocytes

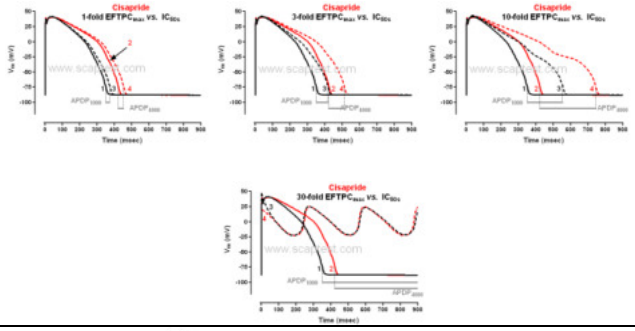


Transmural dispersion of repolarisation

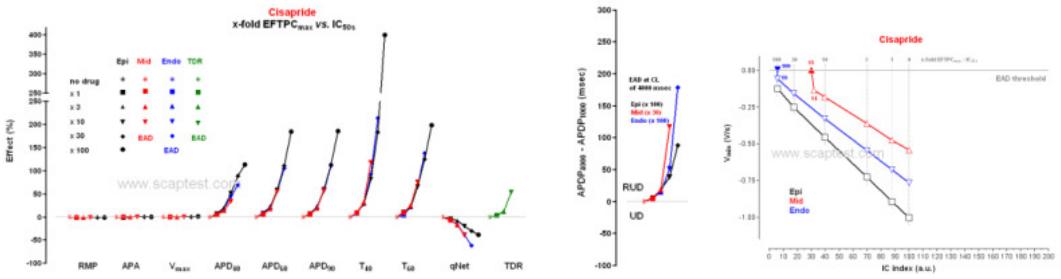


Reverse use dependence on midmyocardial myocytes

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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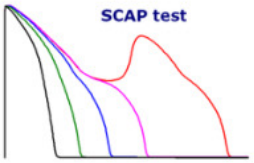


Drug

Citalopram

Serotonin reuptake (SSRI) inhibitor used to treat depression

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 38.0 µM (1.0)
I_{to} : ---- µM (---)
I_{Kr} : 1.1 µM (0.81)
I_{NaL} : ---- µM (---)
I_{Na} : 14.7µM (1.0)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ [1]

0.0271 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] : 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'

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

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= fold slope

TDR and RUD estimation:

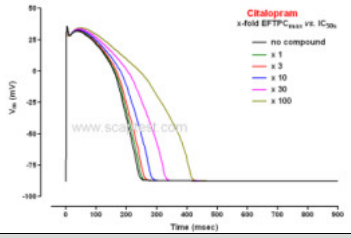
- TDR = APD_{90} mid - APD_{90} epi (at CL of 1000 msec)
- RUD = $APD_{90}P_{x000}$- $APD_{90}P_{1000}$

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

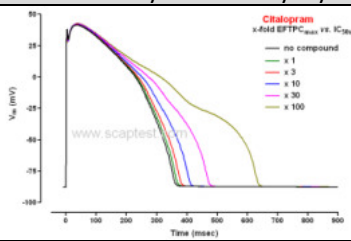
IC index calculation [9]:

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

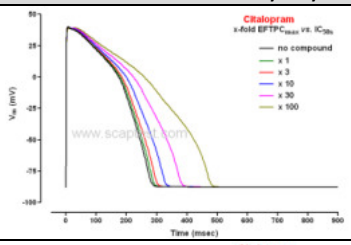
Human epicardial myocytes



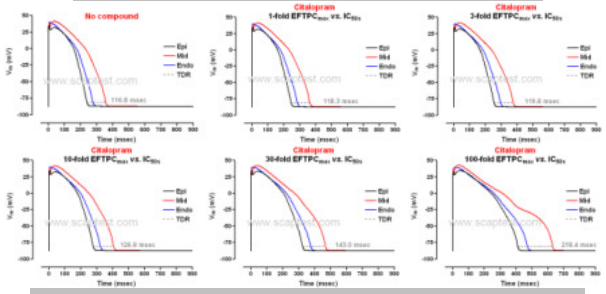
Human midmyocardial myocytes



Human endocardial myocytes

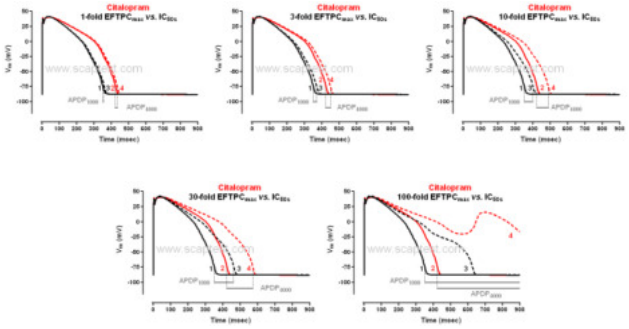


Transmural dispersion of repolarisation

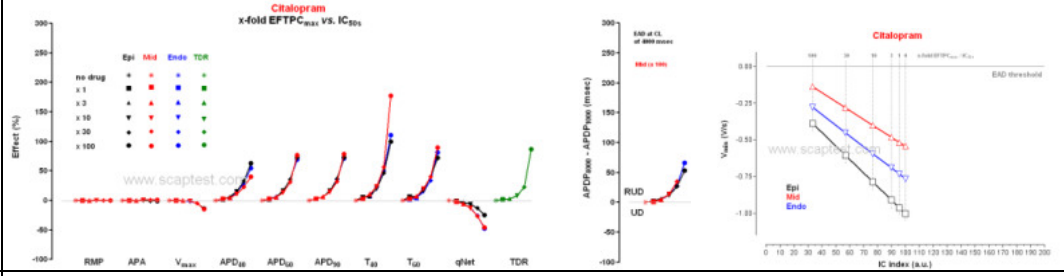


Reverse use dependence on midmyocardial myocytes

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
4. Woosley RL (2015) www.CredibleMeds.org
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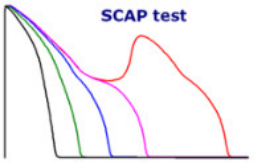
8. Mirams GR et al. (2011) *Cardiovasc. Res.* **91** : 53-61
9. Christophe B & Crumb WJ Jr (2019) *J Pharmacol Toxicol Methods* **96** : 15-26

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 $I_{CaL}+I_{Kr}+I_{Na}+I_{to}+I_{NaL}+I_{K1}$, **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

Clarithromycin

Macolide antibiotic used to treat various bacterial infections

Raw data

IC_{50s} (slope) [1]

I_{CaL} : ---- µM (---)
I_{to} : ---- µM (---)
I_{Kr} : 87.097 µM (1.0)
I_{NaL} : ---- µM (---)
I_{Na} : ---- µM (---)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ [1]

4.011 µM

TdP risk

Redfern [2] : isolated TdP reports (class 4)
Kramer [3] : not reported
CredibleMeds [4] : known risk of TdP (class 1)
CiPA [5] : intermediate risk of TdP (class 2)
WP [6] : 9/3 (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 = fold slope

TDR and RUD estimation:
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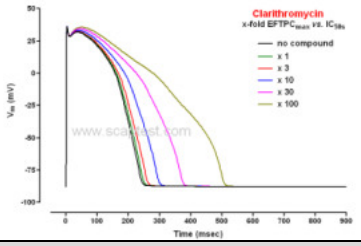
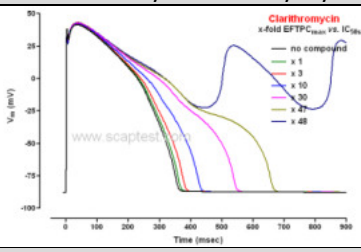
- RUD = $APD_{90}P_{x000}$- $APD_{90}P_{1000}$ where $APD_{90}P_x$ = APD_{90} with - APD_{90} without compound at CL x

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}.

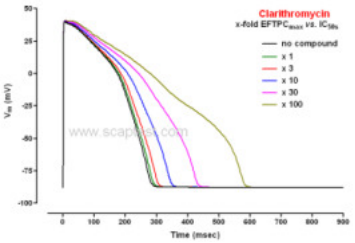
Human epicardial myocytes



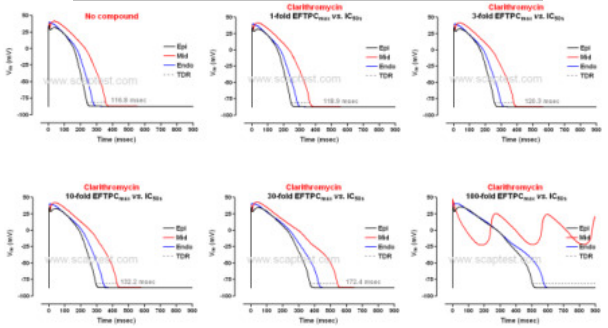
Human midmyocardial myocytes



Human endocardial myocytes

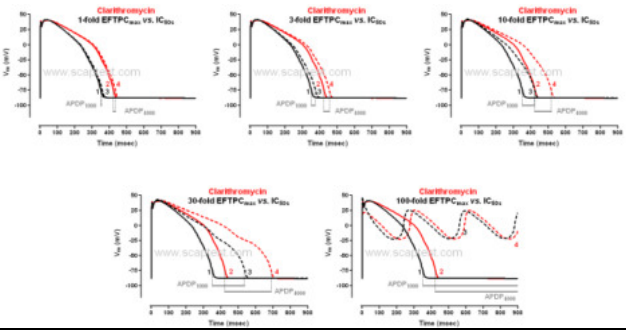


Transmural dispersion of repolarisation

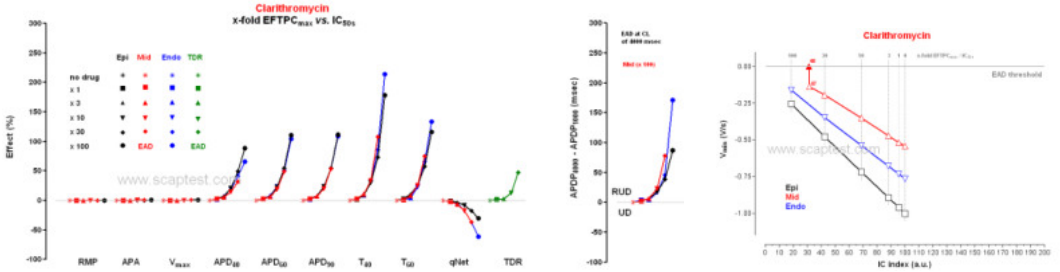


Reverse use dependence on midmyocardial myocytes

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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8. Mirams GR et al. (2011) *Cardiovasc. Res.* **91** : 53-61
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Abbreviations

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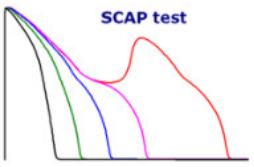

Drug

Clozapine

Non-selective monoamine receptor (5-HT$_2$, D$_2$, α_{1}, α_{2} and H$_1$) antagonist used to treat schizophrenia and risk of suicide
no longer marketed in Finland, Singapore and Norway (Onakpoya et al (2016) *BMC Med.* **14**: 10)

Raw data

IC_{50s} (slope) (1)

I_{CaL} : 3.6 µM (1.0)
I_{Kr} : 2.3 µM (0.97)
I_{Na} : 15.1 µM (1.14)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ (1)

0.071 µM

TdP risk

Redfern (2) : not reported
Kramer (3) : torsadogenic (class 2)
CredibleMeds (4) : possible risk of TdP (class 2)
CiPA (5) : intermediate risk of TdP (class 2)
WP (6) : 4/3 (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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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 = $APD_{90}P_{x1000}$-$APD_{90}P_{1000}$

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
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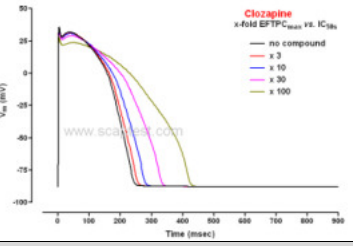
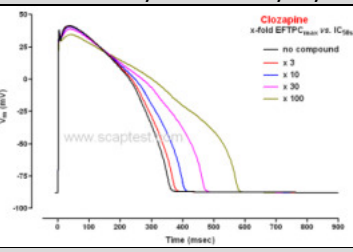
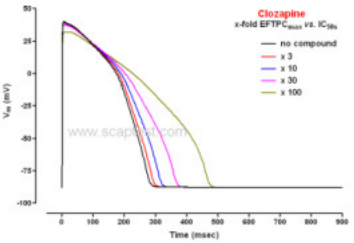
Human epicardial myocytes



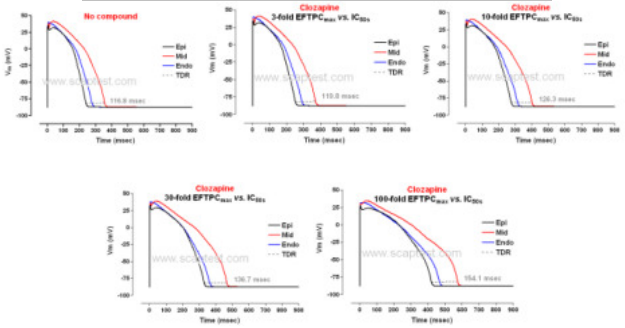
Human midmyocardial myocytes



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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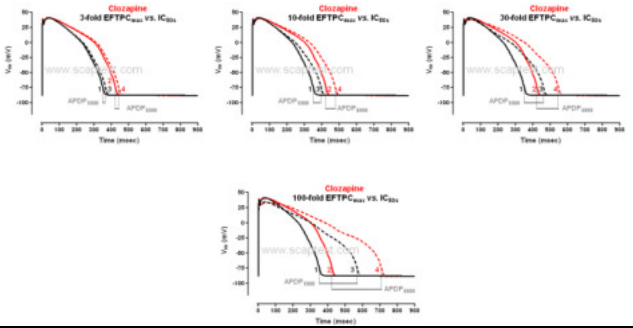
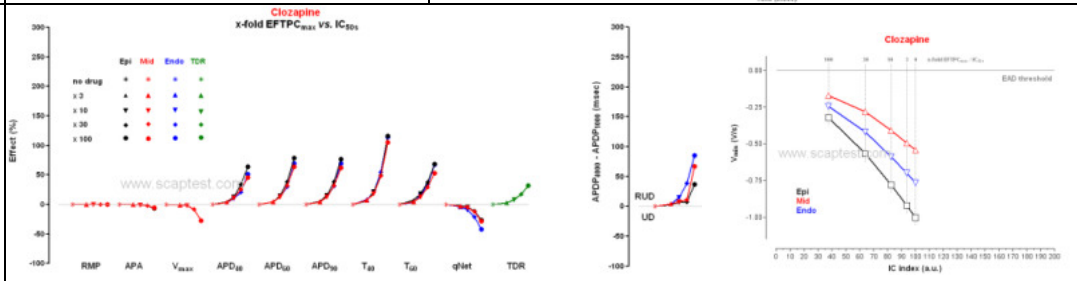


Summary



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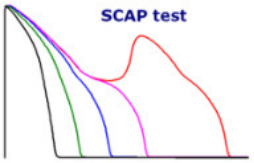

Drug

Darifenacin

Muscarinic M_3 antagonsit used to treat urinary incontinence

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 1584.9 µM (1.0)
I_{Kr} : 0.079 µM (1.0)
I_{Na} : 1.585 µM (1.0)
I_{Ks} : 19.95 µM (1.0)
I_{to} : 12.59 µM (1.0)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ [1]

0.00136 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}

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

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

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
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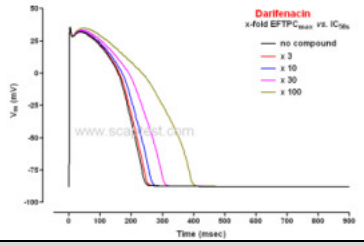
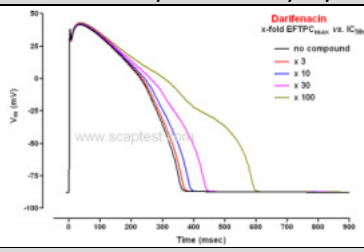
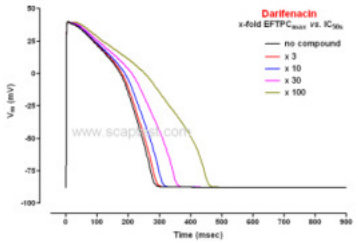
Human epicardial myocytes



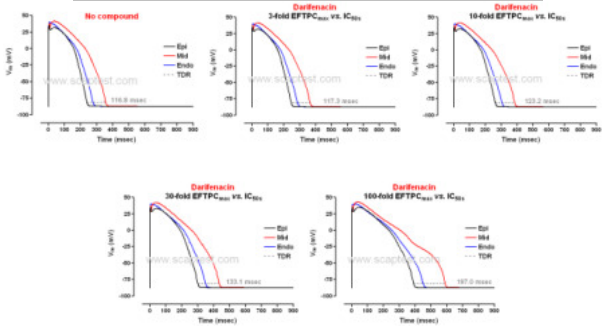
Human midmyocardial myocytes



Human endocardial myocytes

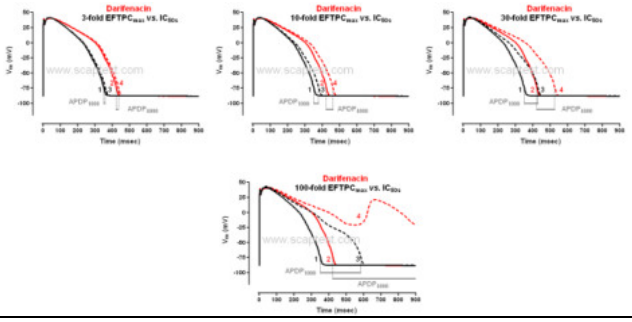


Transmural dispersion of repolarisation

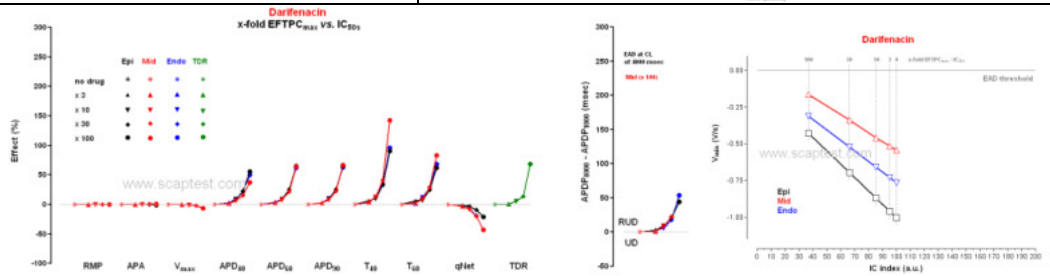


Reverse use dependence on midmyocardial myocytes

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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1. Mirams GR et al. (2014) J.Pharmacol.Tox.Methods 70: 246-254
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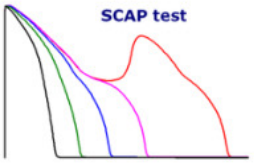
3. Kramer J et al. (2013) *Sci.rep.* **3** : 2100
4. Woosley RL (2015) www.CredibleMeds.org
5. CiPA (2016) www.ilsiextra.org/hesi/science/cardiac/cipa/Project
6. Wiśniowska B et al. (2017) *Drug discovery today* **22** : 10-16
7. O'Hara T et al. (2011) *PLoS Comput. Biol.* **7** : e1002061_8
8. Mirams 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_{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

Darunavir

HIV protease inhibitor used to treat human immunodeficiency virus (HIV) infection

Raw data

IC_{50s} (slope) [1]

I_{CaL} : ---- µM (---)
I_{to} : 100.0 µM (1.0)
I_{Kr} : 158.5 µM (1.0)
I_{NaL} : ---- µM (---)
I_{Na} : 39.81 µM (1.0)
I_{K1} : ---- µM (---)
I_{Ks} : 316.2 µM (1.0)

$EFTPC_{max}$ [1]

0.46338 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}

$$I_j = g\,O(V - E_{ion})$$

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'

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

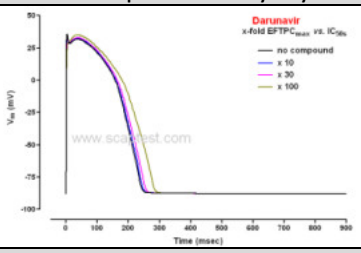
g = maximal conductance of channel 'j'
$g_{control\,j}$ = drug free maximal conductance of channel 'j'
IC50 = 50% of inhibition of a drug for channel 'j'
D= drug concentration (EFTPC for example)
n= fold slope

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

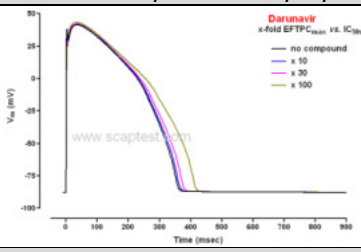
where
$APD_{90}P_x$ = APD_{90} with - APD_{90} without compound at CL x

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}.

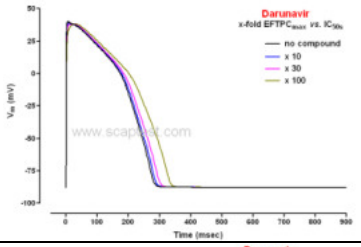
Human epicardial myocytes



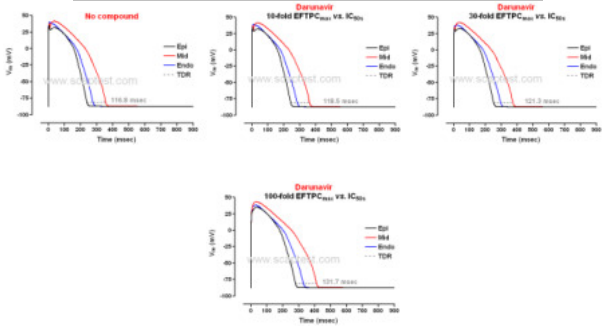
Human midmyocardial myocytes



Human endocardial myocytes

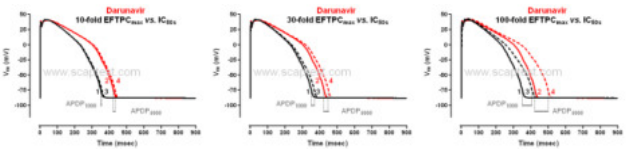


Transmural dispersion of repolarisation

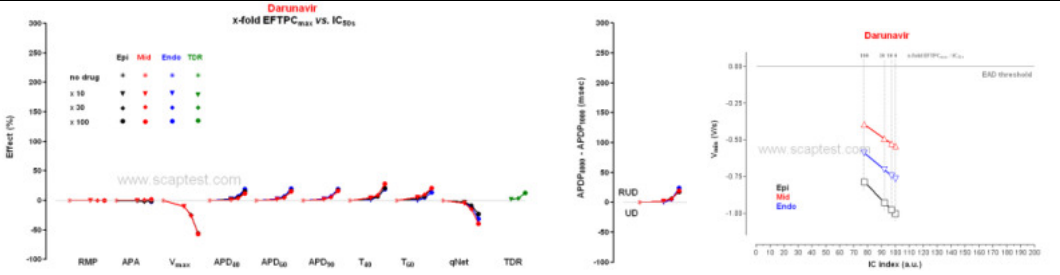


Reverse use dependence on midmyocardial myocytes

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

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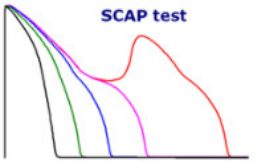


Drug

Dasatinib

Non-selective tyrosine kinase inhibitor used to treat lymphoblastic or chronic myeloid leukemia

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 81.1 µM (1.0)
I_{to} : ---- µM (---)
I_{Kr} : 24.5 µM (1.16)
I_{NaL} : ---- µM (---)
I_{Na} : 76.3 µM (1.43)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ [1]

0.041 µM

TdP risk

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

$I_j = g\,O(V - E_{ion})$ (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)

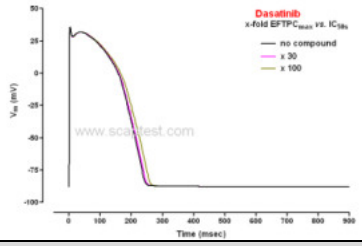
$g_j = g_{control,j}\left[1 + \left(\frac{D}{IC50_j}\right)^n\right]^{-1}$ (g = maximal conductance of channel j; $g_{control,j}$ = drug-free maximal conductance of channel j; IC50 = 50% of inhibition of a drug for channel j; D= drug concentration (EFTPC for example); n = hill slope)

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

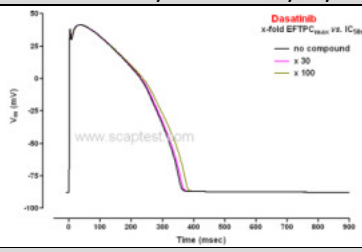
where
$APD_{90}P_x$ = APD_{90} with - APD_{90} without compound at CL x

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}.

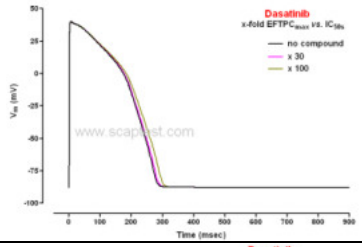
Human epicardial myocytes



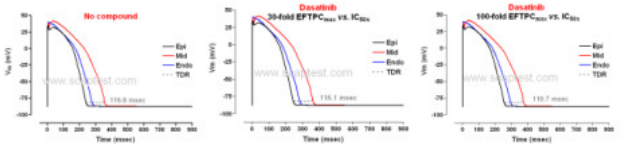
Human midmyocardial myocytes



Human endocardial myocytes

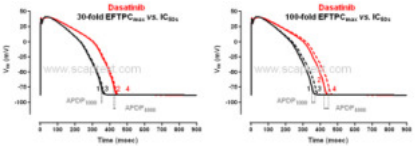


Transmural dispersion of repolarisation

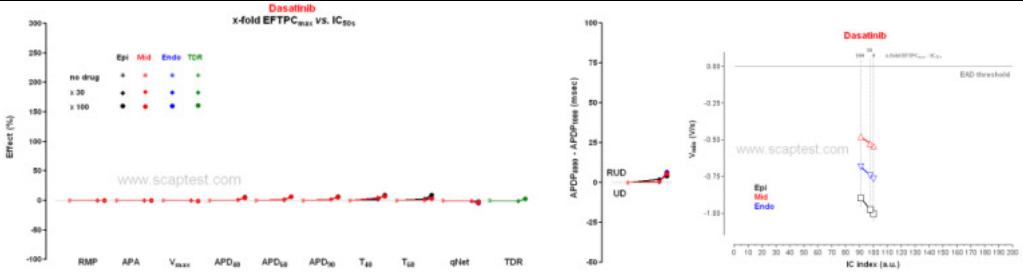


Reverse use dependence on midmyocardial myocytes

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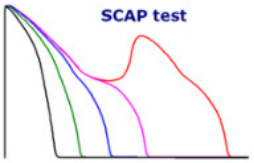


Drug

Deferasirox

Iron chelator used to treat chronic iron overload caused by blood transfusions

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 1000.0 µM (1.0)
I_{to} : 50.12µM (1.0)
I_{Kr} : 3981.1 µM (1.0)
I_{NaL} : ---- µM (---)
I_{Na} : 79.43 µM (1.0)
I_{K1} : ----- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ [1]

0.995 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
- 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'

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

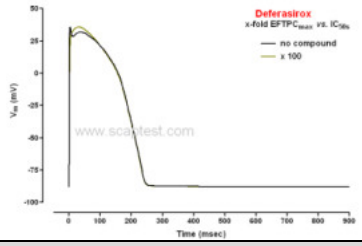
g = maximal conductance of channel 'j'
$g_{control,j}$ = drug-free maximal conductance of channel 'j'
IC50 = 50% of inhibition of a drug for channel 'j'
D= drug concentration (EFTPC for example)
n= fold slope

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

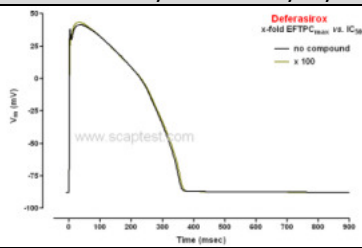
where
$APD_{90}P_x$ = APD_{90} with - APD_{90} without compound at CL x

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}.

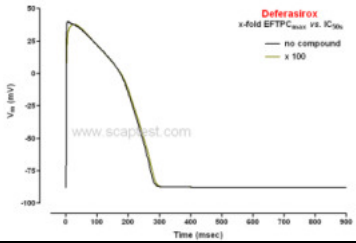
Human epicardial myocytes



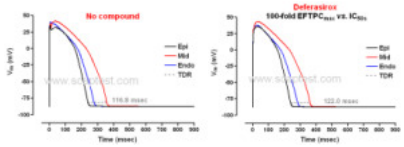
Human midmyocardial myocytes



Human endocardial myocytes

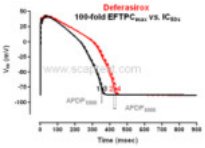


Transmural dispersion of repolarisation



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



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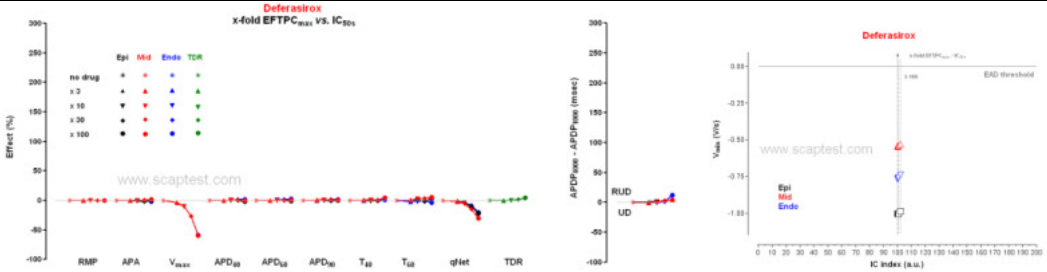

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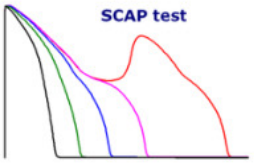

Drug

Desipramine

5-HT and noradrenaline reuptake inhibitor used to treat depression

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 1.709 µM (1.0)
I_{Kr} : 1.390 µM (1.0)
I_{Na} : 1.520 µM (1.0)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ [1]

0.108 µM

TdP risk

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

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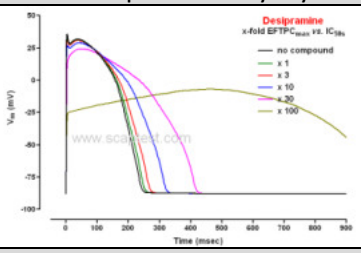
- TDR = APD_{90} mid - APD_{90} epi (at CL of 1000 msec)
- RUD = $APD_{90}P_{x000}$- $APD_{90}P_{1000}$

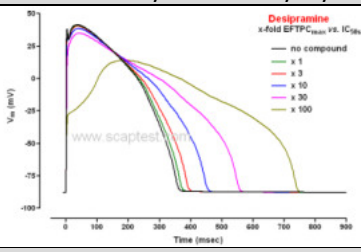
where
$APD_{90}P_x$ = APD_{90} with - APD_{90} without compound at CL x

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}.

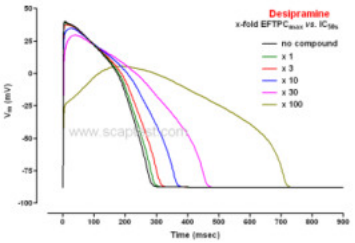
Human epicardial myocytes



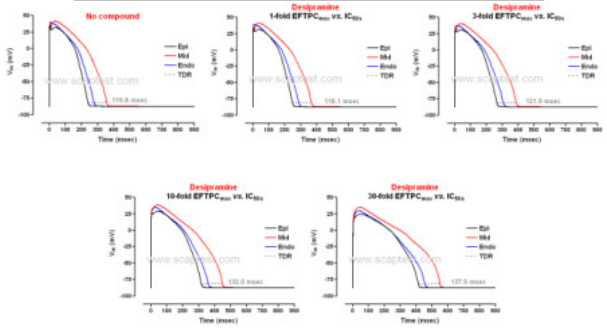
Human midmyocardial myocytes



Human endocardial myocytes

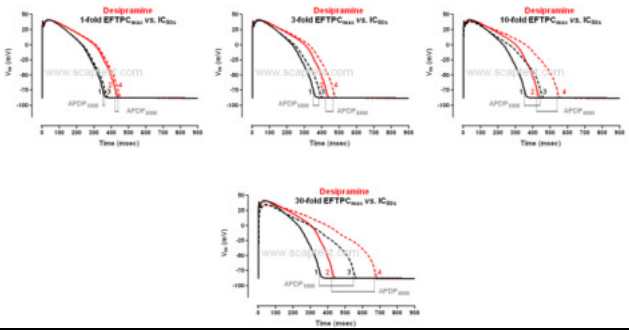


Transmural dispersion of repolarisation

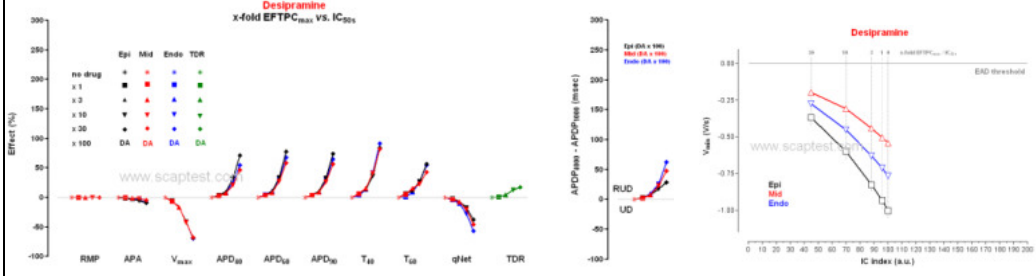


Reverse use dependence on midmyocardial myocytes

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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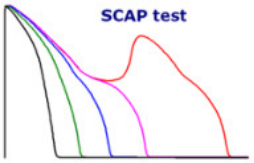
6. Wiśniowska B et al. (2017) *Drug discovery today* **22** : 10-16
7. O'Hara T et al. (2011) *PLoS Comput. Biol.* **7** : e1002061
8. Mirams GR et al. (2011) *Cardiovasc. Res.* **91** : 53-61
9. Christophe B & Crumb WJ Jr (2019) *J Pharmacol Toxicol Methods* **96** : 15-26

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

Desvenlafaxine

5-HT and noradrenaline reuptake inhibitor used to treat depression

Raw data

IC_{50s} (slope) [1]

I_{CaL} : ---- µM (---)
I_{to} : 5011.9 µM (1.0)
I_{Kr} : 251.19 µM (1.0)
I_{NaL} : 0.0 µM (---)
I_{Na} : 199.53 µM (1.0)
I_{K1} : 0.0 µM (---)
I_{Ks}: ---- µM (---)

$EFTPC_{max}$ [1]

2.576 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 = 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)

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

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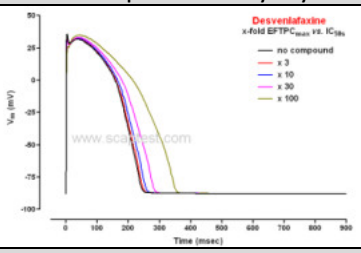
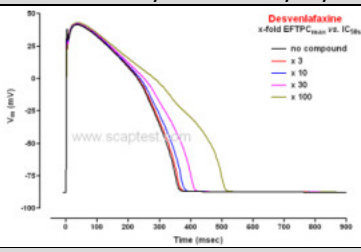
where
$APD_{90}P_x$ = APD_{90} with - APD_{90} without compound at CL x

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}.

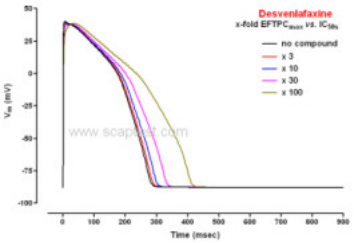
Human epicardial myocytes



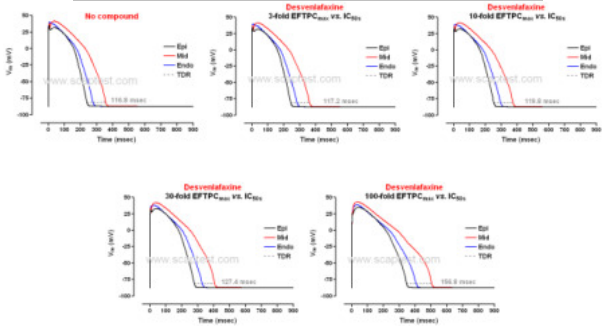
Human midmyocardial myocytes



Human endocardial myocytes

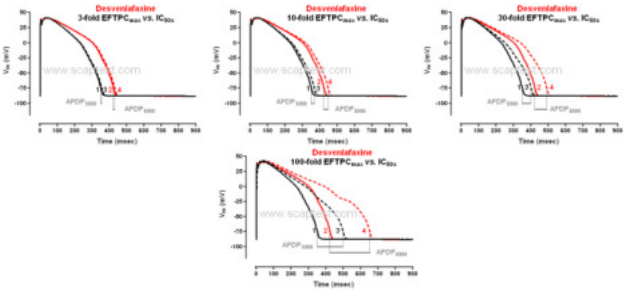


Transmural dispersion of repolarisation

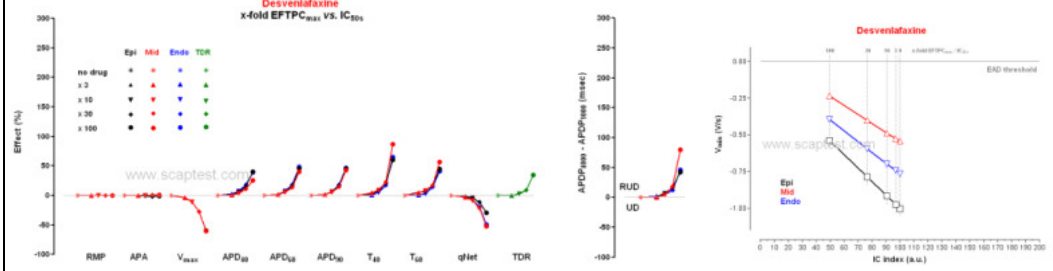


Reverse use dependence on midmyocardial myocytes

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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Abbreviations

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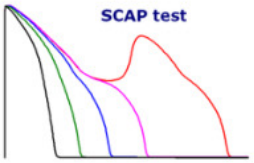


Drug

Diazepam

Gamma aminobutyric acid ($GABA_A$) receptor antagonist used to treat panic disorders, severe anxiety, alcohol withdrawal and seizures

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 30.5 µM (0.89)
I_{Kr} : 53.2 µM (1.07)
I_{Na} : 306.4 µM (1.0)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ [1]

0.029 µM

TdP risk

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

$I_j = g\,O(V - E_{ion})$ (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)

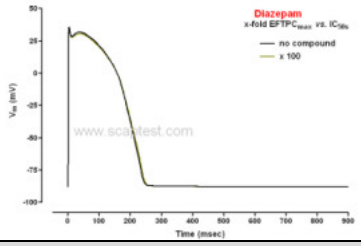
$g_j = g_{control,j}\left[1 + \left(\frac{D}{IC50_j}\right)^n\right]^{-1}$ (g = maximal conductance of channel j; $g_{control,j}$ = drug-free maximal conductance of channel j; IC50 = 50% of inhibition of a drug for channel j; D= drug concentration (EFTPC for example); n= hill slope)

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

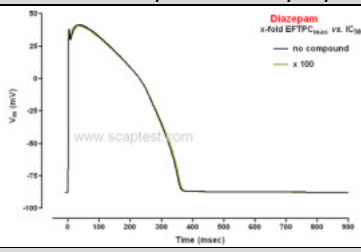
where
$APD_{90}P_x$ = APD_{90} with - APD_{90} without compound at CL x

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

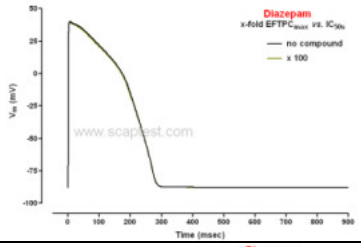
Human epicardial myocytes



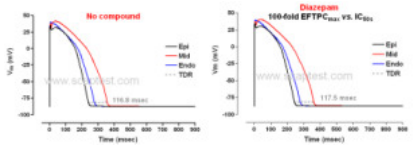
Human midmyocardial myocytes



Human endocardial myocytes

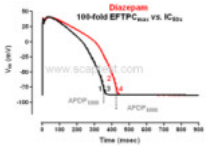


Transmural dispersion of repolarisation

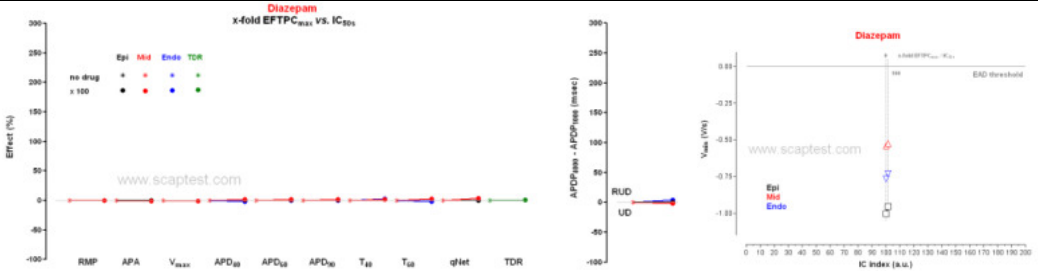


Reverse use dependence on midmyocardial myocytes

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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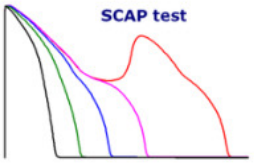

Drug

Diltiazem

L-type slow Ca^{++} channel ($Ca_v1.2$) blocker used to treat hypertension and chronic stable angina

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 0.76 µM (1.14)
I_{to} : ---- µM (---)
I_{Kr} : 13.2 µM (1.16)
I_{NaL} : ---- µM (---)
I_{Na} : 22.4 µM (1.29)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ [1]

0.122 µM

TdP risk

Redfern [2] : no published report of TdP (class 5)
Kramer [3] : non-torsadogenic (class 1)
CredibleMeds [4] : conditional risk of TdP (class 3)
CiPA [5] : very low or no risk of TdP (class 3)
WP [6] : 0/9 (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= fold slope

TDR and RUD estimation:
- TDR = APD_{90} mid - APD_{90} epi (at CL of 1000 msec)
- RUD = $APD_{90}P_{x400}$- $APD_{90}P_{1000}$

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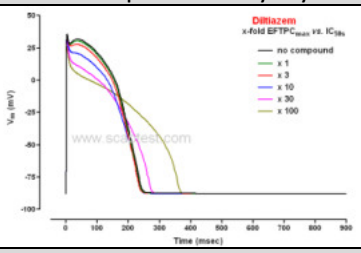
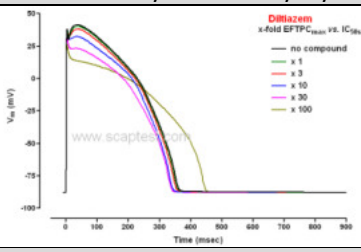
$APD_{90}P_x$ = APD_{90} with - APD_{90} without compound at CL x

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}.

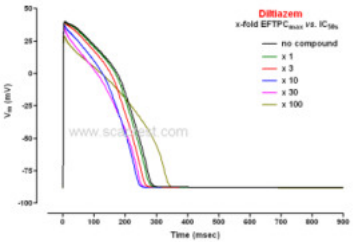
Human epicardial myocytes



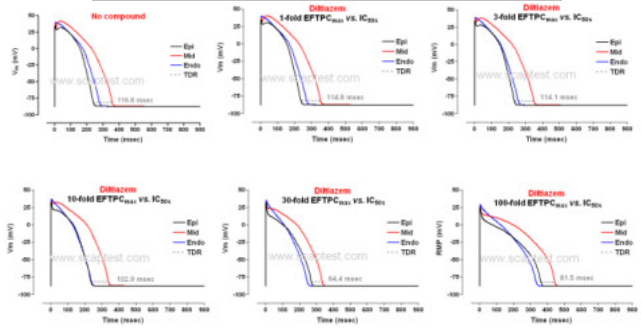
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarisation



Reverse use dependence on midmyocardial myocytes

1 - CL 1000 msec without compound
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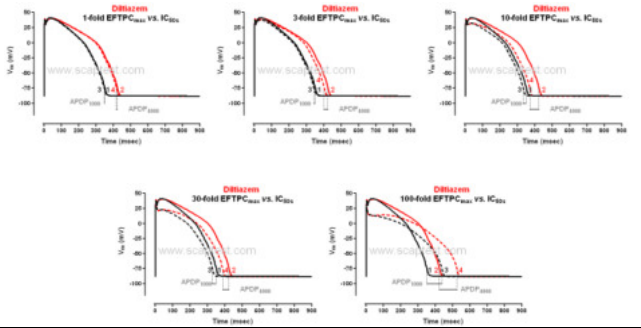
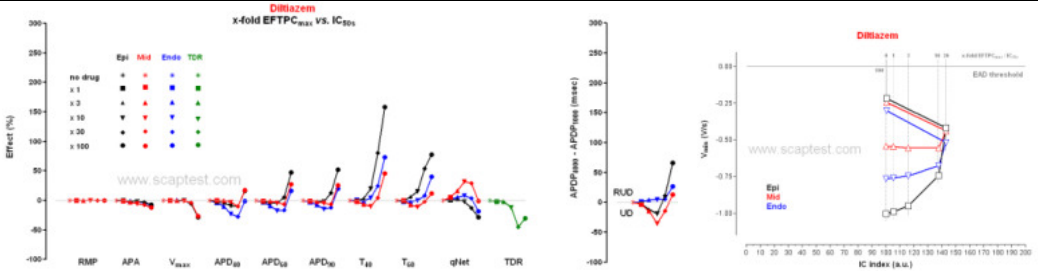


Summary



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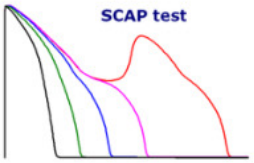
4. Woosley RL (2015) www.CredibleMeds.org
5. CiPA (2016) www.ilsiextra.org/hesi/science/cardiac/cipa/Project
6. Wiśniowska B et al. (2017) *Drug discovery today* **22** : 10-16
7. O'Hara T et al. (2011) *PLoS Comput. Biol.* **7** : e1002061_8
8. Mirams GR et al. (2011) *Cardiovasc. Res.* **91** : 53-61
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_{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

Diphenhydramine

Histamine H_1 receptor antagonist used to treat seasonal allergies and various other allergic reactions

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 228.0 µM (1.0)
I_{Kr} : 5.2 µM (1.0)
I_{Na} : 41.0 µM (1.0)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ [1]

0.034 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] : 3/5 (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}

$$I_j = g\,O(V - E_{ion})$$

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'

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

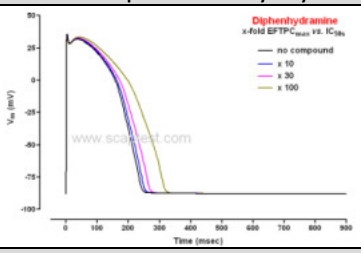
g = maximal conductance of channel 'j'
$g_{control\,j}$ = drug free maximal conductance of channel 'j'
IC50 = 50% of inhibition of a drug for channel 'j'
D= drug concentration (EFTPC for example)
n= hill slope

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

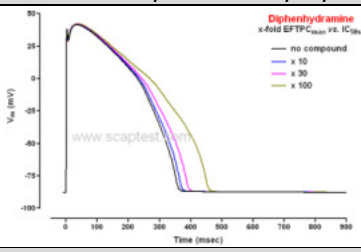
where
$APD_{90}P_x$ = APD_{90} with - APD_{90} without compound at CL x

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}.

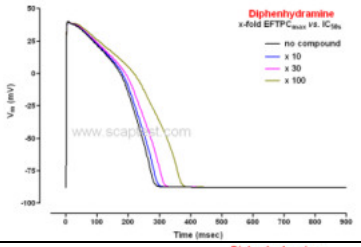
Human epicardial myocytes



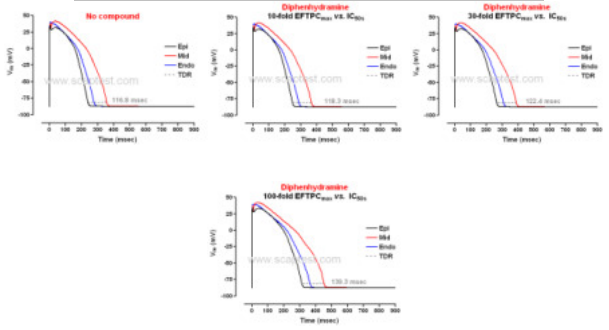
Human midmyocardial myocytes



Human endocardial myocytes

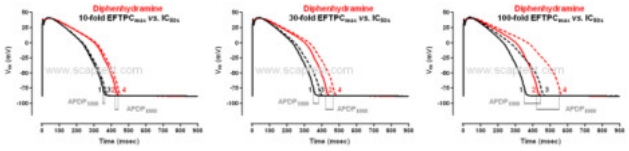


Transmural dispersion of repolarisation

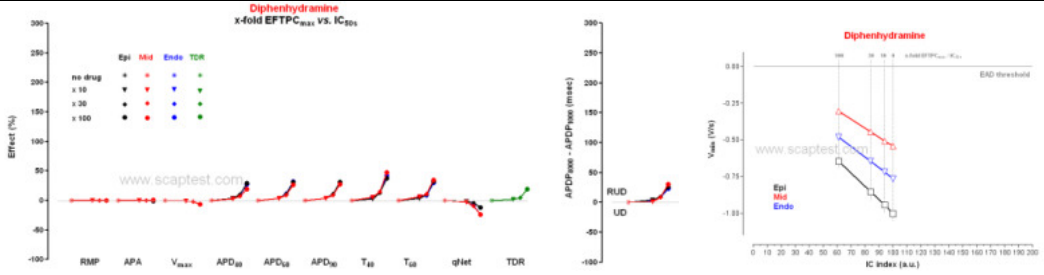


Reverse use dependence on midmyocardial myocytes

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

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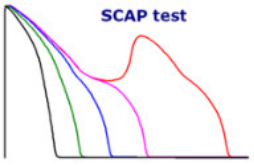


Drug

Disopyramide

Fast Na^+ channel ($Na_v1.5$) blocker used as class IA antiarrhythmic to treat ventricular arrhythmias

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 1036.7 µM (1.0)
I_{to} : ---- µM (---)
I_{Kr} : 14.4 µM (0.91)
I_{NaL} : ---- µM (---)
I_{Na} : 168.4 µM (1.09)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ [1]

0.742 µM

TdP risk

Redfern [2] : large but acceptable TdP risk (class 1)
Kramer [3] : torsadogenic (class 2)
CredibleMeds [4] : known risk of TdP (class 1)
CiPA [5] : high risk of TdP (class 1)
WP [6] : 10/0 (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}

$I_j = g\,O(V - E_{ion})$

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

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

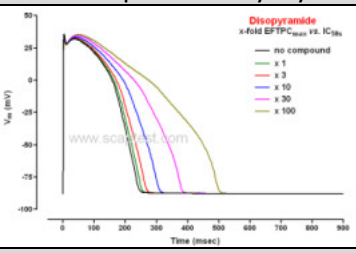
g = maximal conductance of channel j
$g_{control,j}$ = drug free maximal conductance of channel j
IC50 = 50% of inhibition of a drug for channel j
D= drug concentration (EFTPC for example)
n= hill slope

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

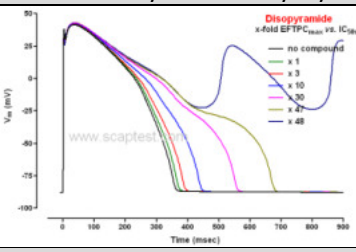
where
$APD_{90}P_x$ = APD_{90} with - APD_{90} without compound at CL x

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}.

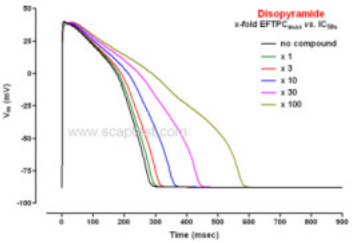
Human epicardial myocytes



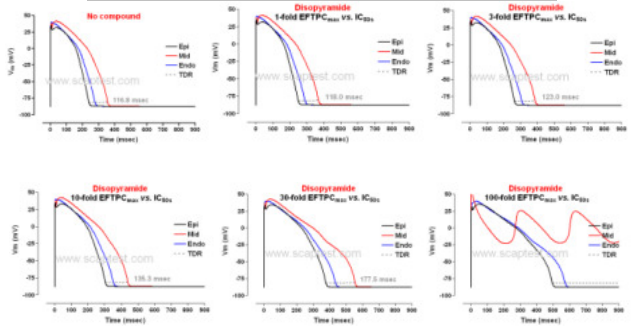
Human midmyocardial myocytes



Human endocardial myocytes

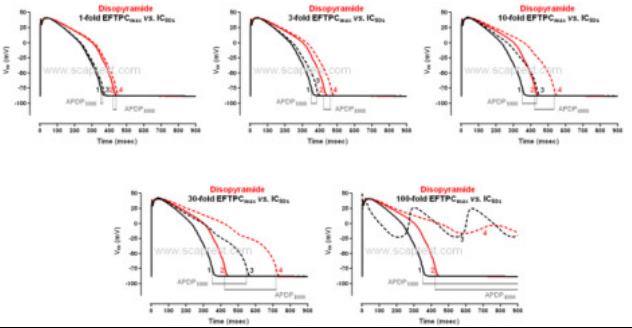


Transmural dispersion of repolarisation

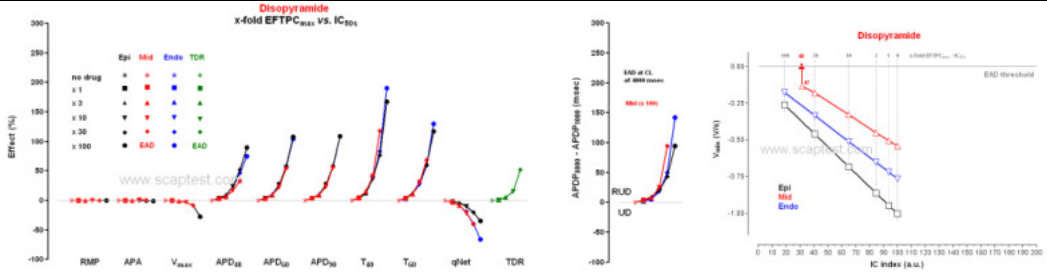


Reverse use dependence on midmyocardial myocytes

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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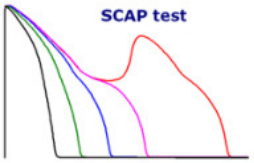

Drug	**Dobutamine** β_1-adrenoceptor agonist used to treat cardiac decompensation

Raw data

IC_{50s} (slope) [1]		$EFTPC_{max}$ [1]	TdP risk
I_{CaL} : 55.147 µM (1.00)	I_{to} : ---- µM (---)	0.03819 µM	Redfern [2] : not reported
I_{Kr} : 15.0 µM (1.17)	I_{NaL} : ---- µM (---)		Kramer [3] : not reported
I_{Na} : 117.187µM (1.00)	I_{K1} : ---- µM (---)		CredibleMeds [4] : drug to avoid in congenital long QT
I_{Ks} : 53.571 µM (2.28)			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_{rev} = 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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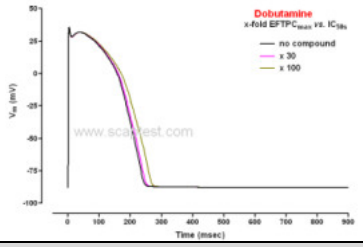
TDR and RUD estimation:
- TDR = APD_{90} mid - APD_{90} epi (at CL of 1000 msec)
- RUD = $APD_{90}P_{x000}$- $APD_{90}P_{1000}$

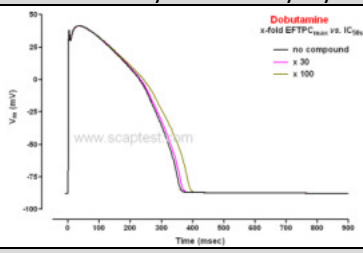
where
$APD_{90}P_x$ = APD_{90} with - APD_{90} without compound at CL x

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}

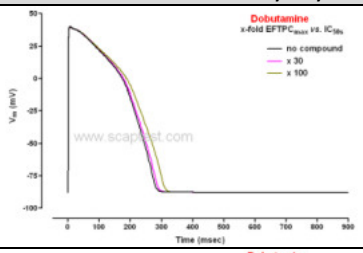
Human epicardial myocytes



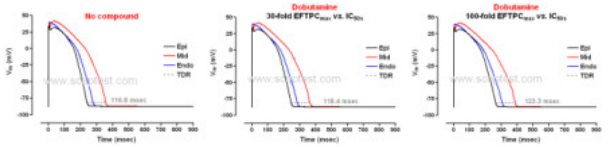
Human midmyocardial myocytes



Human endocardial myocytes

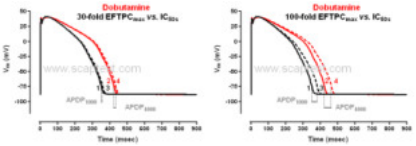


Transmural dispersion of repolarisation

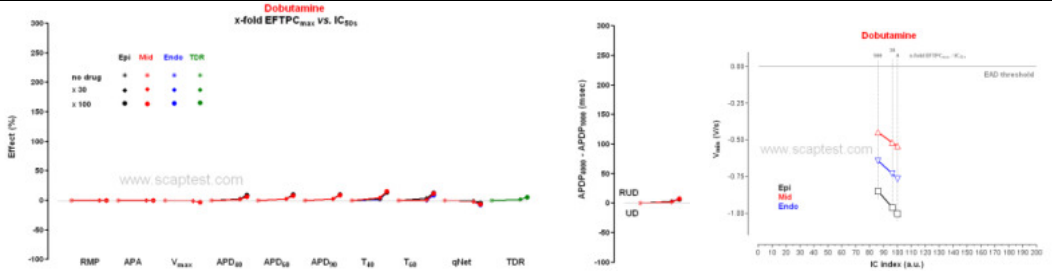


Reverse use dependence on midmyocardial myocytes

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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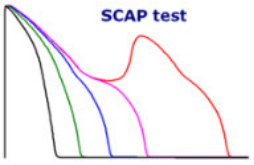


Drug

Dofetilide

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

Raw data

IC_{50s} (slope) [1]

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

$EFTPC_{max}$ [1]

0.002 µM

TdP risk

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

Results

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

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

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

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

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'

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

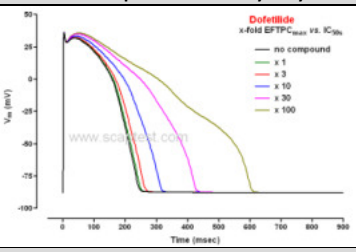
g_j = maximal conductance of channel 'j'
$g_{control\_j}$ = drug-free maximal conductance of channel 'j'
IC50 = 50% of inhibition of a drug for channel 'j'
D= drug concentration (EFTPC for example)
n= hill slope

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

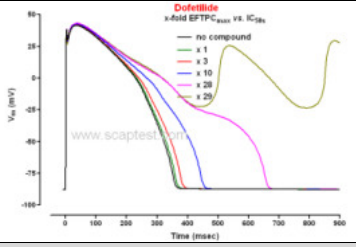
where
$APD_{90}P_x$ = APD_{90} with - APD_{90} without compound at CL x

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}

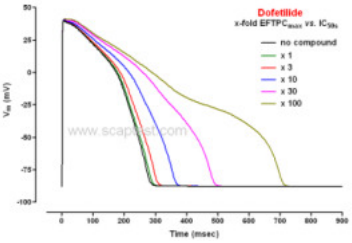
Human epicardial myocytes



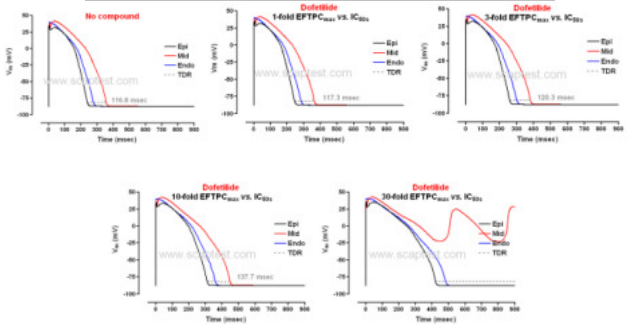
Human midmyocardial myocytes



Human endocardial myocytes

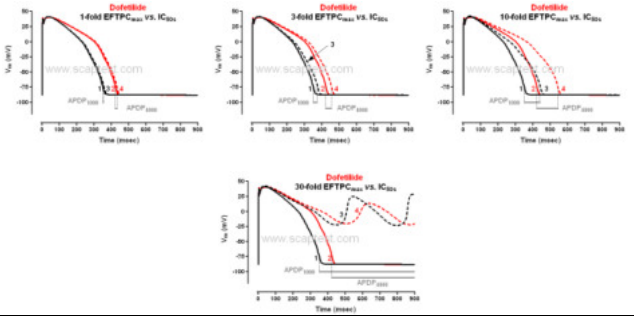


Transmural dispersion of repolarisation

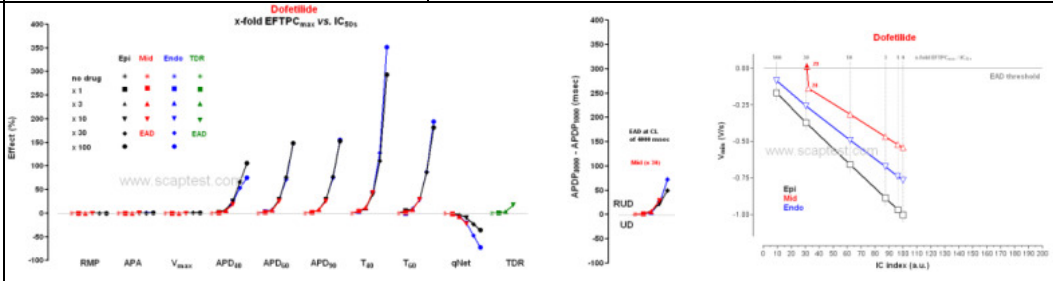


Reverse use dependence on midmyocardial myocytes

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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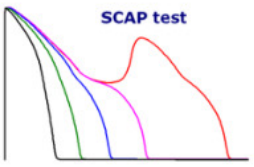
1. Kramer J et al. (2013) *Sci.rep.* **3** : 2100
2. Redfern WS et al. (2003) *Cardiovasc. Res.* **58** : 32-45
3. Kramer J et al. (2013) *Sci.rep.* **3** : 2100
4. Woosley RL (2015) www.CredibleMeds.org
5. CiPA (2016) www.ilisiextra.org/hesi/science/cardiac/cipa/Project
6. Wiśniowska B et al. (2017) *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_{to}+I_{Na}+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

Dolasetron

Serotonin 5-HT$_3$ receptor antagonist used as antinauseant and antiemetic
no longer marketed in Germany (Onakpoya et al (2016) *BMC Med.* **14**: 10)

Raw data

IC$_{50s}$ (slope) [1]

I$_{CaL}$: ---- µM (---)
I$_{Kr}$: 5.95 µM (1.0)
I$_{Na}$: 38.0 µM (1.0)
I$_{Ks}$: ---- µM (---)
I$_{to}$: ---- µM (---)
I$_{NaL}$: ---- µM (---)
I$_{K1}$: ---- µM (---)

EFTPC$_{max}$ [1]

0.36 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 = 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:

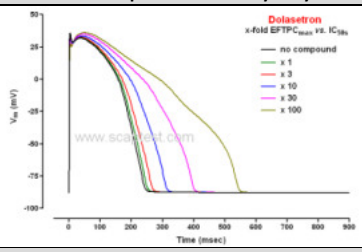
- TDR = APD$_{95}$ mid - APD$_{95}$ epi (at CL of 1000 msec)
- RUD = APD$_{90}$P$_{x000}$-APD$_{90}$P$_{1000}$

where
APD$_{90}$P$_x$ = APD$_{90}$ with - APD$_{90}$ without compound at CL x

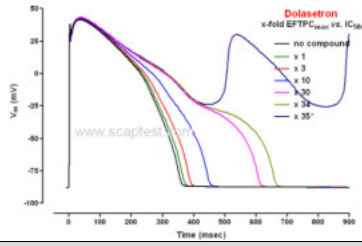
IC index calculation [9]:

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

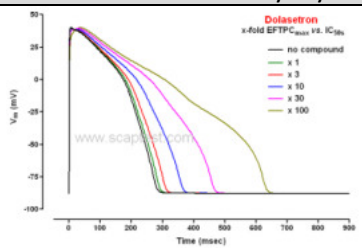
Human epicardial myocytes



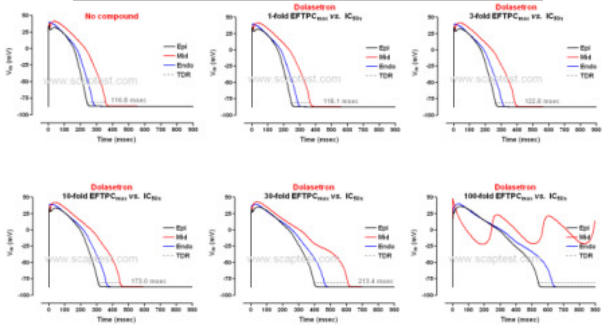
Human midmyocardial myocytes



Human endocardial myocytes

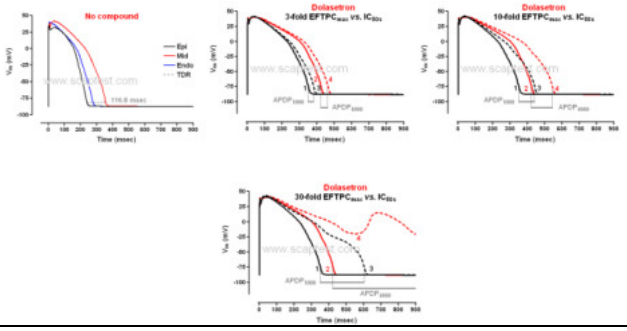


Transmural dispersion of repolarisation

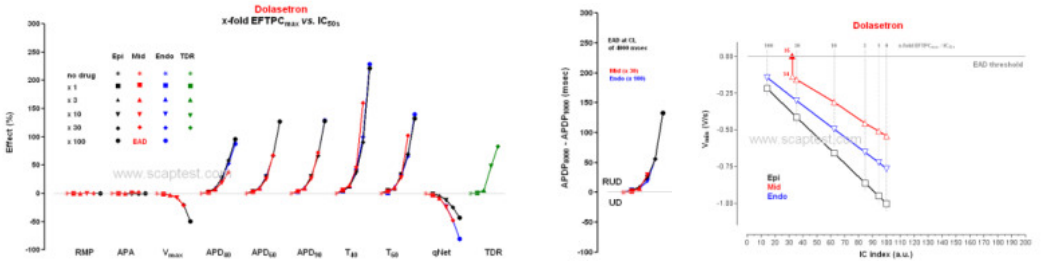


Reverse use dependence on midmyocardial myocytes

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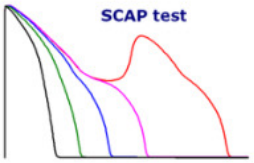
9. Christophe B & Crumb WJ Jr (2019) *J Pharmacol Toxicol Methods* **96** ; 15-26

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

Domperidone

Dopamine D_2 and D_3 receptors antagonist used as antiemetic and prokinetic agent
no longer marketed worldwide (Onakpoya et al (2016) *BMC Med.* **14**: 10)

Raw data

IC_{50s} (slope) [1]

I_{CaL} : ---- µM (---)
I_{Kr} : 0.160 µM (1.0)
I_{Na} : 5.6 µM (1.0)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ [1]

0.027 µM

TdP risk

Redfern [2] : isolated reports of TdP (class 4)
Kramer [3] : not reported
CredibleMeds [4] : known risk of TdP (class 1)
CiPA [5] : intermediate risk pf TdP (class 2)
WP [6] : 5/2 (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'
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TDR and RUD estimation:

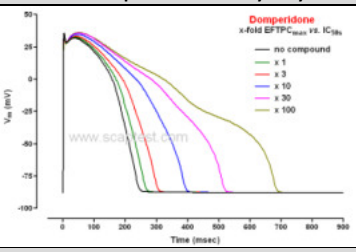
- TDR = APD_{90} mid - APD_{90} epi (at CL of 1000 msec)
- RUD = $APD_{90}P_{x000}$-$APD_{90}P_{1000}$

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

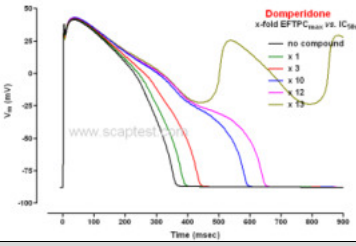
IC index calculation [9]:

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

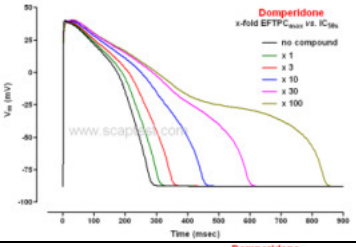
Human epicardial myocytes



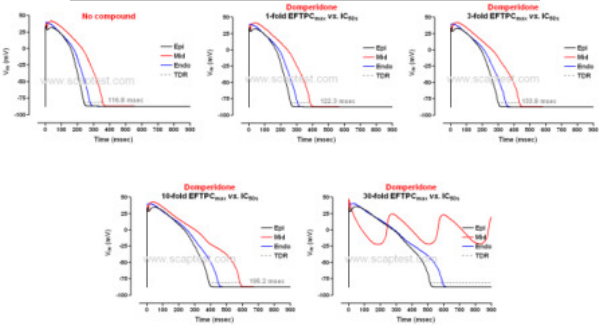
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarisation



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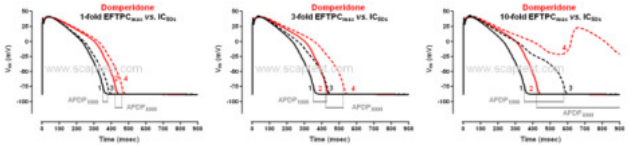
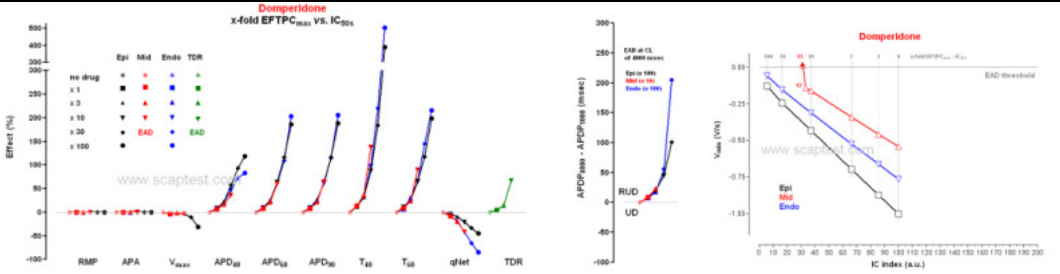


Summary



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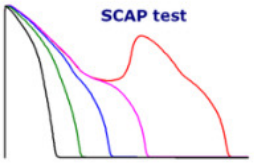


Drug

Donepezil

Acetylcholinesterase enzyme inhibitor used to treat behavioural and cognitive effects of Alzheimer's disease or other type of dementia

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 34.3 µM (0.83)
I_{Kr} : 0.70 µM (0.98)
I_{Na} : 38.5 µM (1.0)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ [1]

0.003 µM

TdP risk

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

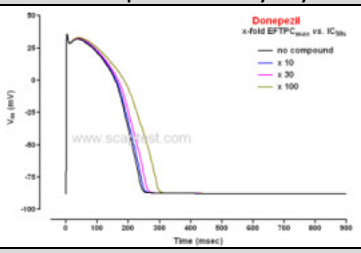
$g_j = g_{control,j}\left[1 + \left(\frac{D}{IC50 \cdot f}\right)^n\right]^{-1}$ (g = maximal conductance of channel j; $g_{control,j}$ = drug free maximal conductance of channel j; IC50 = 50% of inhibition of a drug for channel j; D= drug concentration (EFTPC for example); n= hill slope)

TDR and RUD estimation:
- TDR = APD_{90} mid - APD_{90} epi (at CL of 1000 msec)
- RUD = $APD_{90}P_{x1000}$- $APD_{90}P_{1000}$

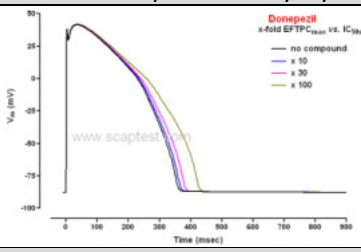
where
$APD_{90}P_x$ = APD_{90} with - APD_{90} without compound at CL x

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}.

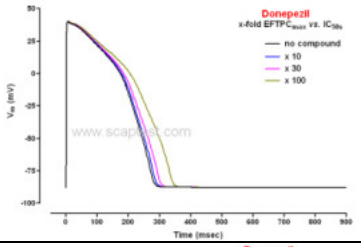
Human epicardial myocytes



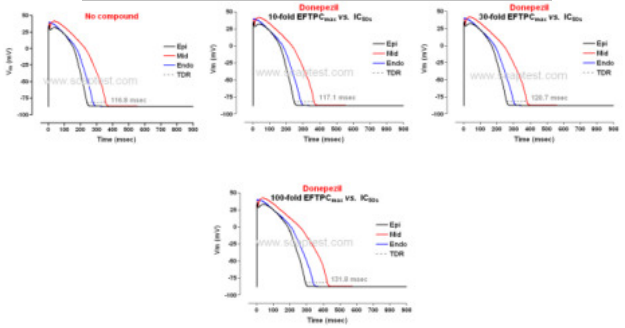
Human midmyocardial myocytes



Human endocardial myocytes

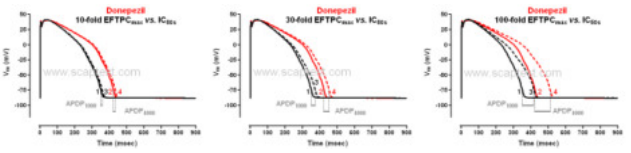


Transmural dispersion of repolarisation

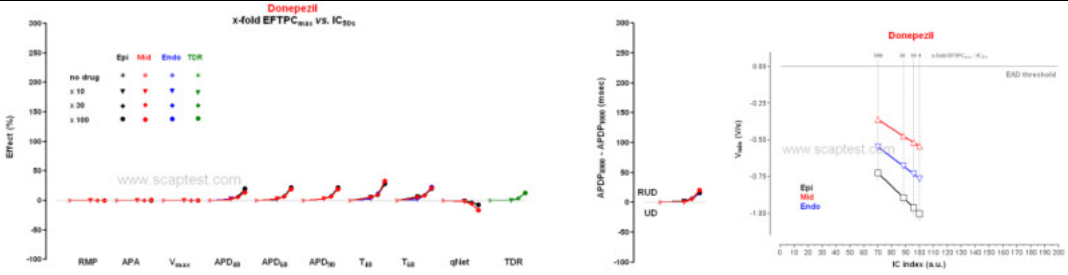


Reverse use dependence on midmyocardial myocytes

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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5. CIPA (2016) www.lhsiextra.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

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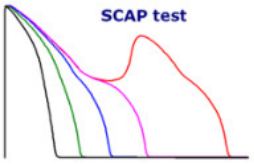


Drug

Doripenem

Penem class of antibiotic used to treat complicated intra-abdominal and urinary tract bacterial infections

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 2.0 µM (1.0)
I_{Kr} : 5011.9 µM (1.0)
I_{Na} : 1584.9 µM (1.0)
I_{Ks} : 316.2 µM (1.0)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ [1]

72.1206 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
- 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}

$I_j = g\,O(V - E_{ion})$

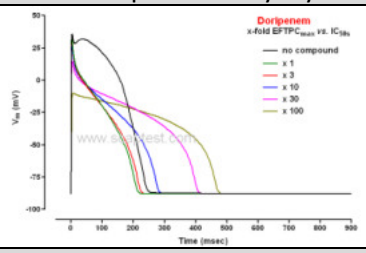
$g_j = g_{control,j}\left[1 + \left(\frac{D}{IC50_j}\right)^n\right]^{-1}$

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

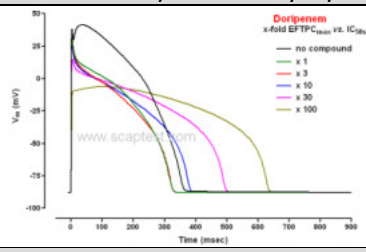
where
$APD_{90}P_x$ = APD_{90} with - APD_{90} without compound at CL x

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}.

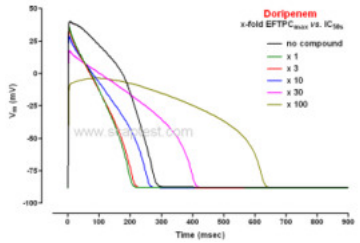
Human epicardial myocytes



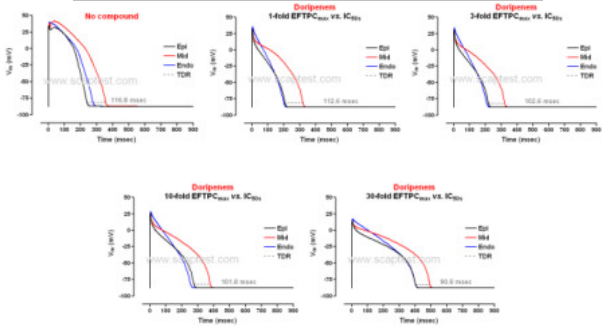
Human midmyocardial myocytes



Human endocardial myocytes

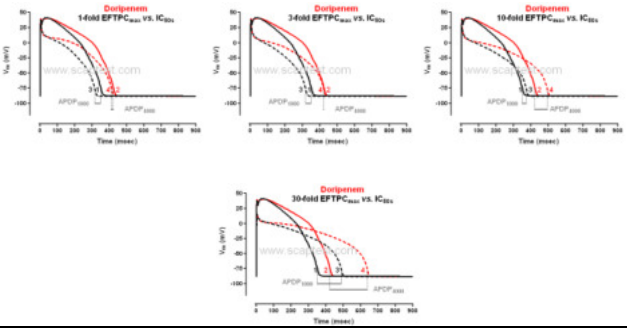


Transmural dispersion of repolarisation

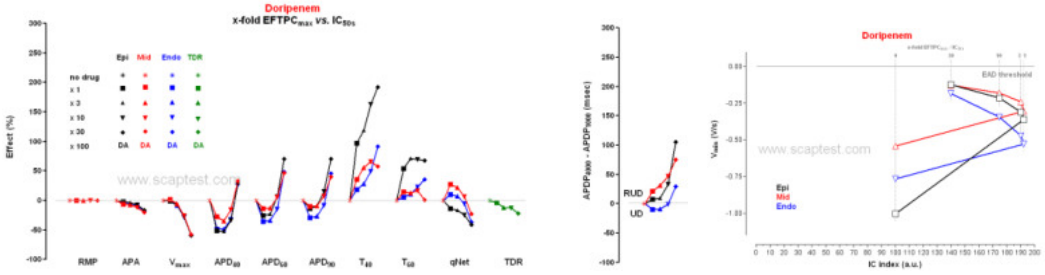


Reverse use dependence on midmyocardial myocytes

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

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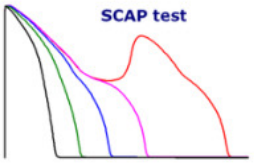


Drug

Doxorubicin

Cytotoxic anthracycline antibiotic used to treat various cancer and Kaposi's sarcoma

Raw data

IC_{50s} (slope) [1]

I_{CaL} : ---- µM (---)
I_{to} : ---- µM (---)
I_{Kr} : 1000.0 µM (1.0)
I_{NaL} : ---- µM (---)
I_{Na} : ---- µM (---)
I_{K1} : ---- µM (---)
I_{Ks} : 4.786 µM (1.0)

$EFTPC_{max}$ [1]

4.646 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] : 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' $G_{control,j}$= 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

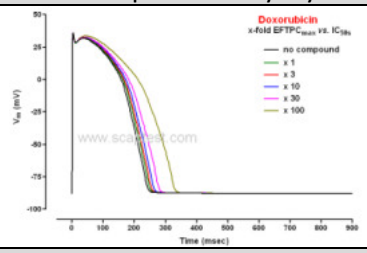
TDR and RUD estimation:

- 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

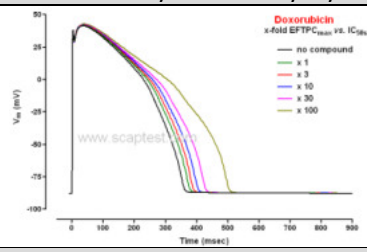
IC index calculation [9]:

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

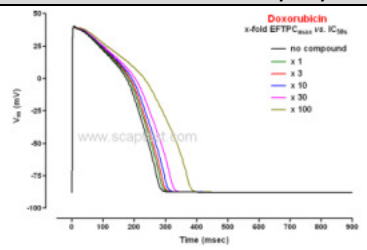
Human epicardial myocytes



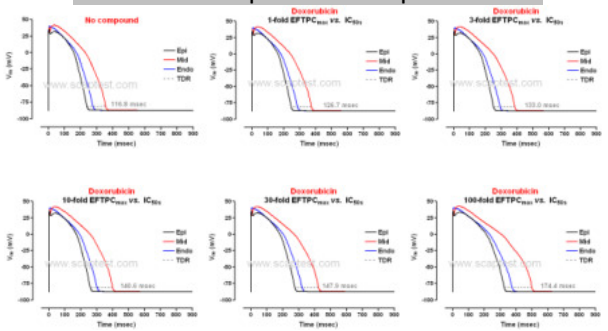
Human midmyocardial myocytes



Human endocardial myocytes

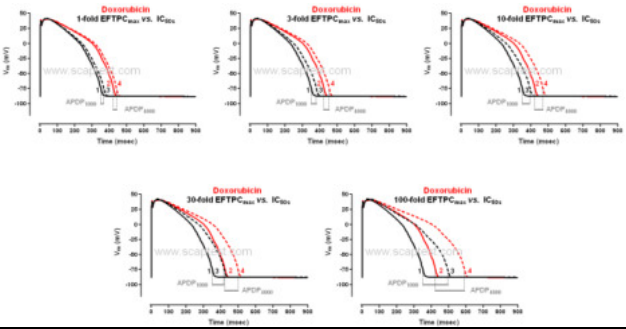


Transmural dispersion of repolarisation

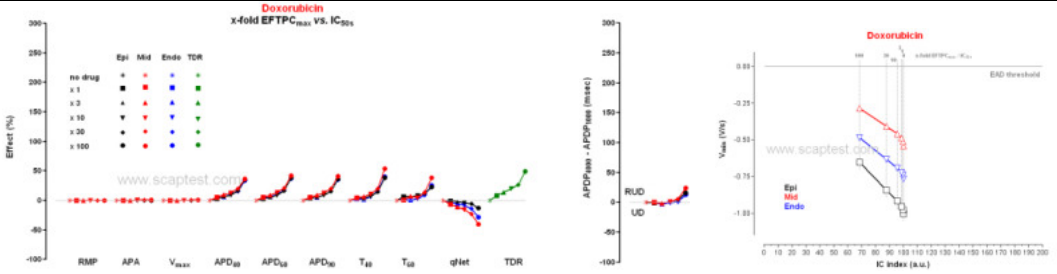


Reverse use dependence on midmyocardial myocytes

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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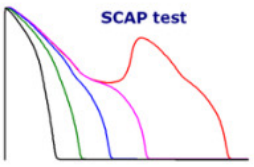

Drug

Dronedarone

Multichannel cardiac channel blocker used as class III antiarrhythmic to reduce risk in case of paroxysmal or persistent atrial fibrillation

Raw data

IC_{50s} (slope) (1)

I_{CaL} : 0.4 µM (1.0)
I_{Kr} : 0.059 µM (1.0)
I_{Na} : 0.7 µM (1.0)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ (1)

0.0018 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) : 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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- 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

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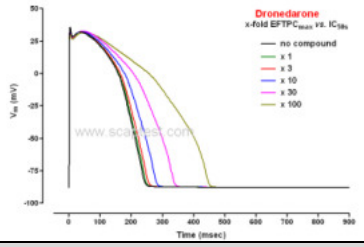
- RUD = $APD_{90}P_{4000}$-$APD_{90}P_{1000}$
  where
  $APD_{90}P_x$ = APD_{90} with - APD_{90} without compound at CL x

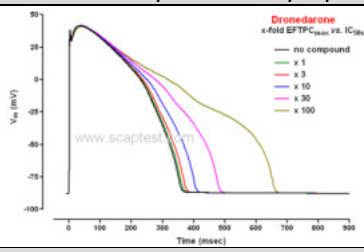
IC index calculation (9):

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

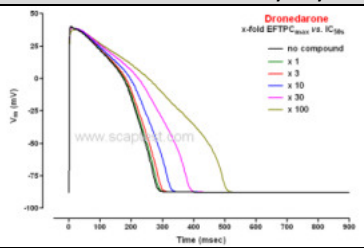
Human epicardial myocytes



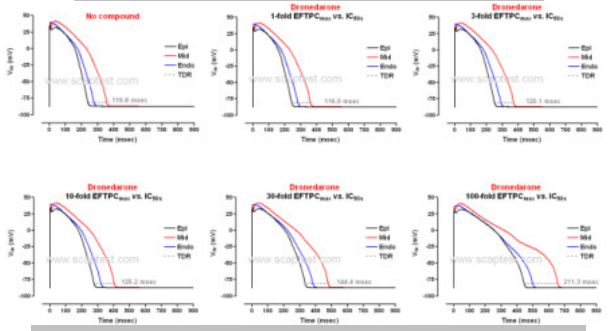
Human midmyocardial myocytes



Human endocardial myocytes

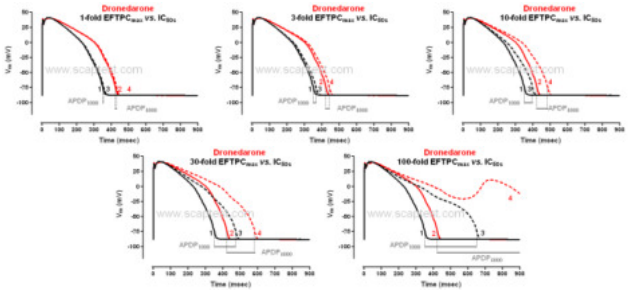


Transmural dispersion of repolarisation

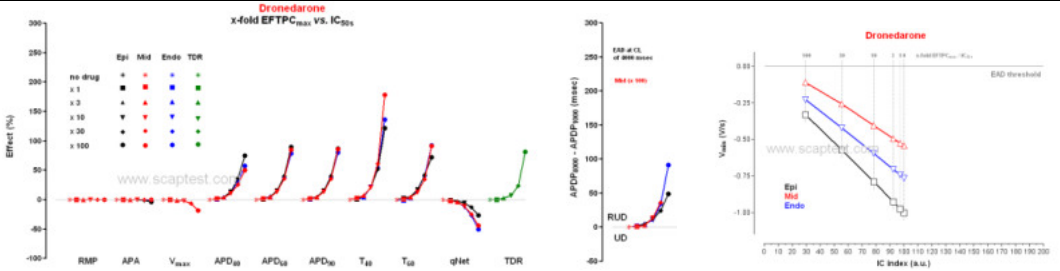


Reverse use dependence on midmyocardial myocytes

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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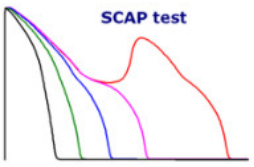

Drug

Droperidol

Dopamine D_2 receptor antagonist used to treat nausea and vomiting
no longer marketed in UK and Indonesia (Onakpoya et al (2016) *BMC Med.* **14**: 10))

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 7.6 µM (1.16)
I_{Kr} : 0.06 µM (1.10)
I_{Na} : 22.7 µM (1.24)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ [1]

0.016 µM

TdP risk

Redfern [2] : unacceptable risk of TdP (class 2)
Kramer [3] : torsadogenic (class 2)
CredibleMeds [4] : known risk of TdP (class 1)
CiPA [5] : intermediate risk of TdP (class 2)
WP [6] : 11/0 (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
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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 = 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:

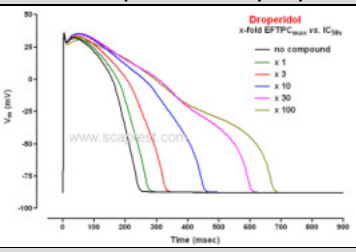
- TDR = APD_{90} mid - APD_{90} epi (at CL of 1000 msec)
- RUD = $APD_{90}P_{4000}$-$APD_{90}P_{1000}$

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

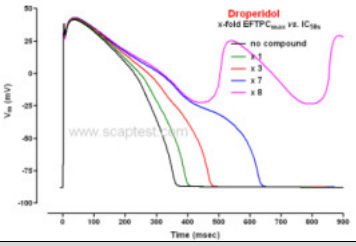
IC index calculation [9]:

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

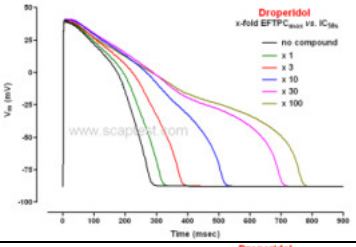
Human epicardial myocytes



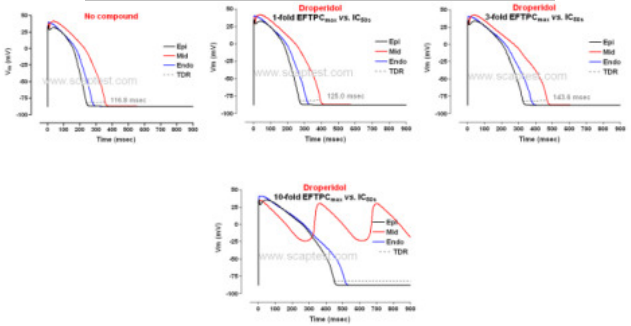
Human midmyocardial myocytes



Human endocardial myocytes

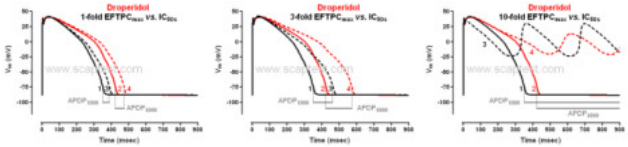


Transmural dispersion of repolarisation

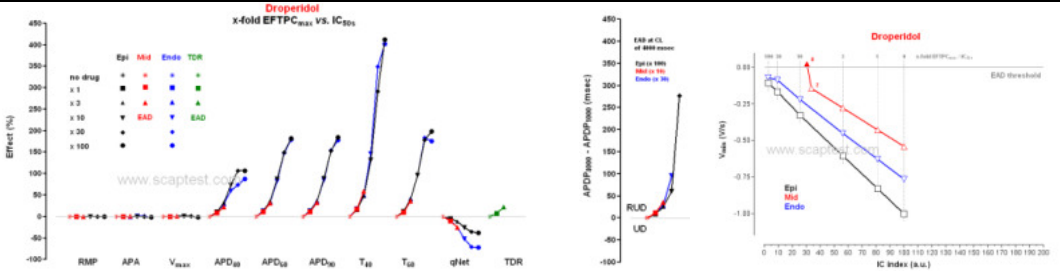


Reverse use dependence on midmyocardial myocytes

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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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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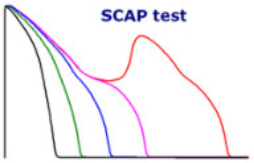

Drug

Duloxetine

5-HT and noradrenaline reuptake inhibitor used to treat anxiety disorder, neuropathic pain, osteoarthritis and stress incontinence

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 2.8 µM (1.41)
I_{to} : ---- µM (---)
I_{Kr} : 3.8 µM (1.39)
I_{NaL} : ---- µM (---)
I_{Na} : 5.1 µM (1.66)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ [1]

0.016 µM

TdP risk

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

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
- 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}

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

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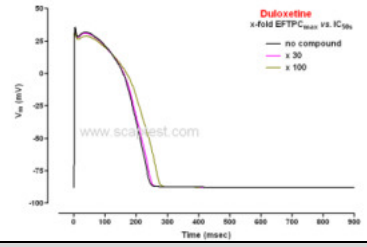
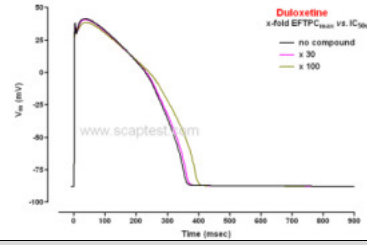
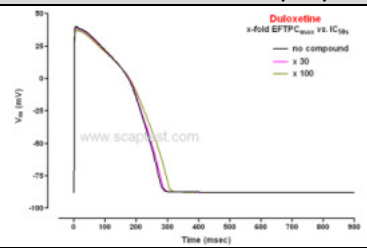
Human epicardial myocytes



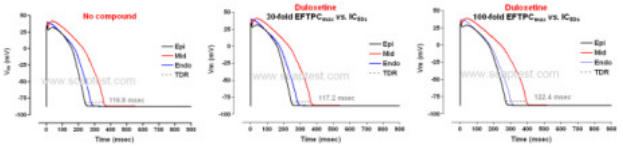
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarisation



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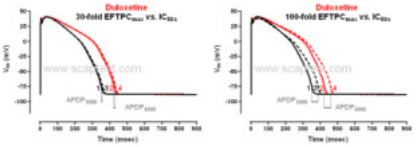

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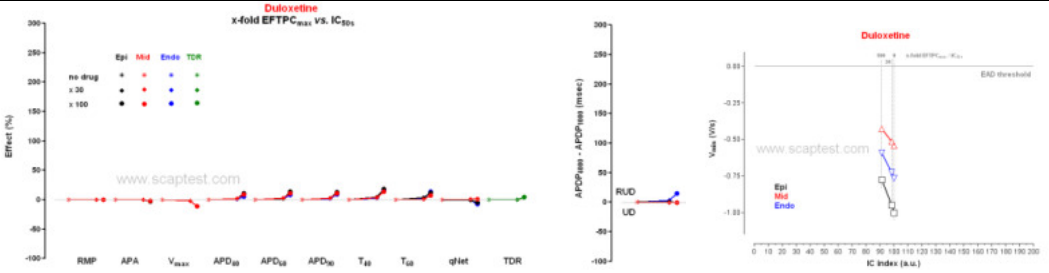

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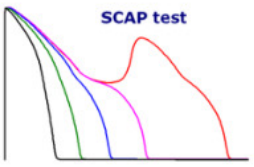

Drug

E-4031

Voltage-gated K^+ channel ($K_v11.1$) blocker used in Class III antiarrhythmic studies

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 713.7 µM (0.454)
I_{to} : ---- µM (---)
I_{Kr} : 0.026 µM (1.996)
I_{NaL} : ---- µM (---)
I_{Na} : 737.3 µM (0.334)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ [1]

0.00567 µM

TdP risk

Redfern [2] : not reported
Kramer [3] : not reported
CredibleMeds [4] : not reported
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
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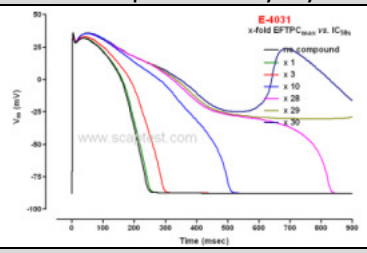
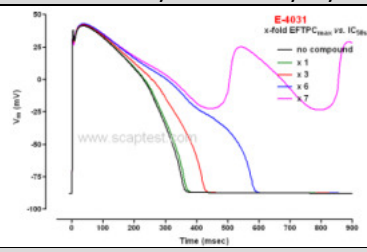
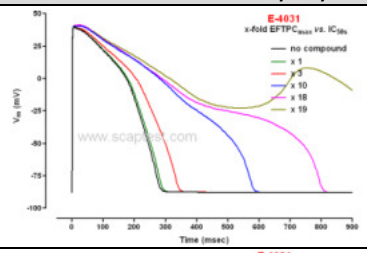
Human epicardial myocytes



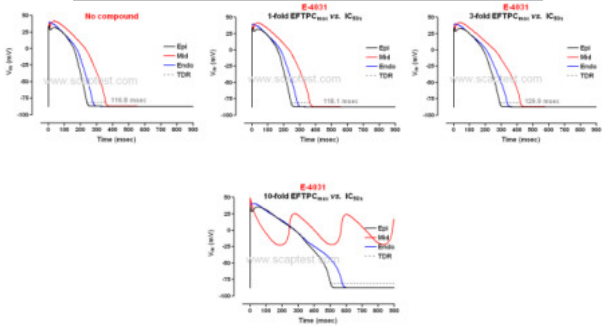
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarisation



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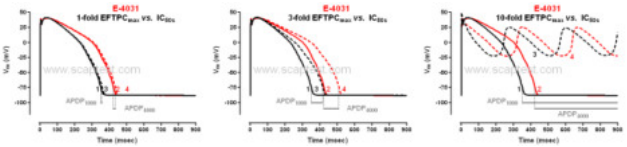

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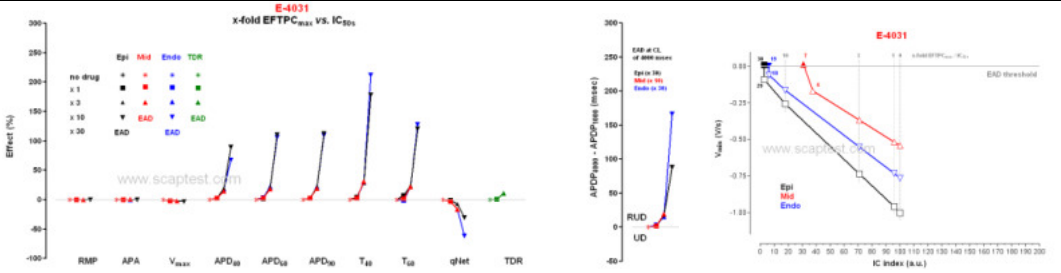

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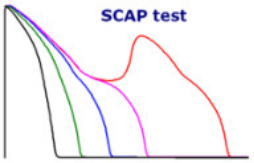

Drug

Ebastine

Histamine H_1 receptor antagonist used to treat allergic rhinitis and urticaria

Raw data

IC_{50s} (slope) [1]

I_{CaL} : ---- µM (---)
I_{Kr} : 0.724 µM (1.0)
I_{Na} : ---- µM (---)
I_{Ks} : 0.794 µM (1.0)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ [1]

0.00014 µM

TdP risk

Redfern [2] : no published report of TdP (class 5)
Kramer [3] : not reported
CredibleMeds [4] : not reported
CiPA [5] : not reported
WP [6] : 0/3 (TdP+/TdP-)

Results

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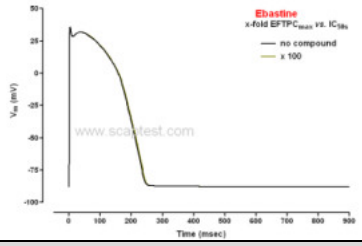
- RUD = $APD_{90}P_{4000}$- $APD_{90}P_{1000}$

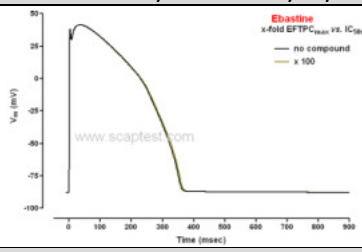
where
$APD_{90}P_x$ = APD_{90} with - APD_{90} without compound at CL x

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

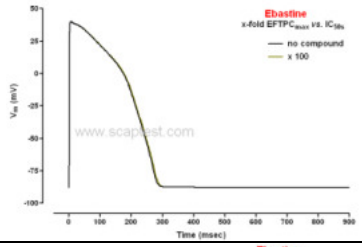
Human epicardial myocytes



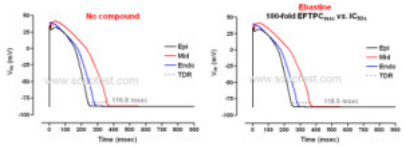
Human midmyocardial myocytes



Human endocardial myocytes

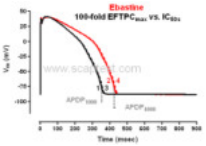


Transmural dispersion of repolarisation

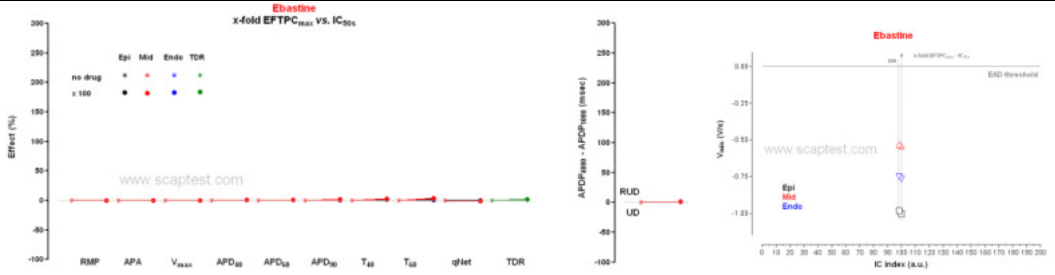


Reverse use dependence on midmyocardial myocytes

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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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
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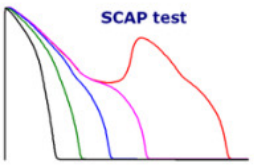
Abbreviations

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

Eltrombopag

Thrombopoietin receptor agonist used to treat thrombocytopenia or aplastic anemia

Raw data

IC_{50s} (slope) [1]

I_{CaL} : --- µM (---)
I_{to} : 1584.89 µM (1.0)
I_{Kr} : 0.631 µM (1.0)
I_{NaL} : --- µM (---)
I_{Na} : 158.49 µM (1.0)
I_{K1} : --- µM (---)
I_{Ks} : --- µM (---)

$EFTPC_{max}$ [1]

0.11481 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 = 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'

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

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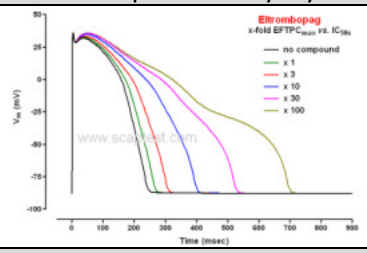
- TDR = APD_{90} mid - APD_{90} epi (at CL of 1000 msec)
- RUD = $APD_{90}P_{4000}$-$APD_{90}P_{1000}$

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

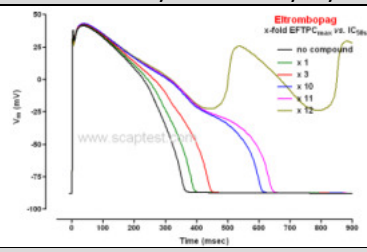
IC index calculation [9]:

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

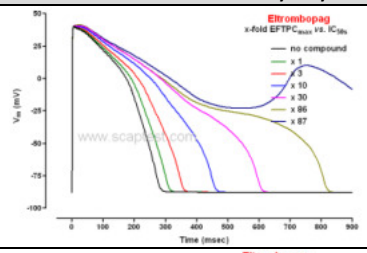
Human epicardial myocytes



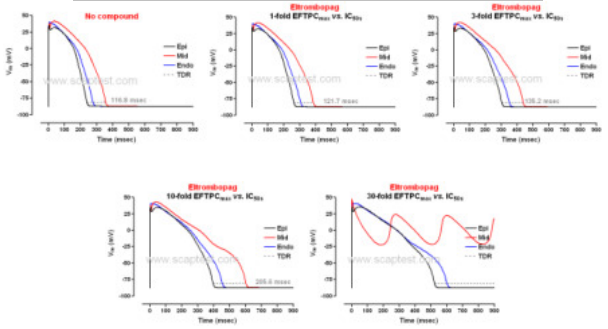
Human midmyocardial myocytes



Human endocardial myocytes

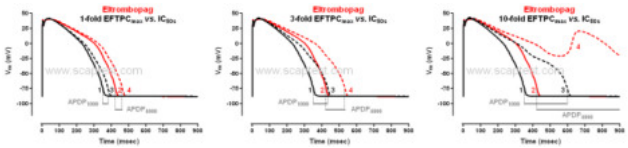


Transmural dispersion of repolarisation

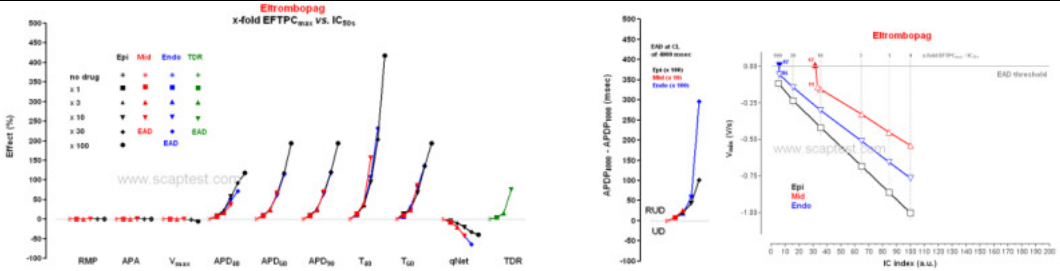


Reverse use dependence on midmyocardial myocytes

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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Abbreviations

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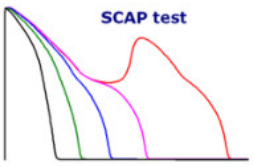

Drug

Encainide

Voltage-gated Na^+ channel ($Na_v1.5$) blocker used to treat atrial or ventricular fibrillation, atrial flutter and ventricular tachycardia
no longer marketed in UK (Onakpoya et al (2016) *BMC Med.* **14**: 10)

Raw data

IC_{50s} (slope) (1)

I_{CaL} : ---- µM (---)
I_{Kr} : 5.42 µM (1.0)
I_{Na} : 11.2 µM (1.0)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ (1)

0.061 µM

TdP risk

Redfern (2) : no published report of TdP (class 5)
Kramer (3) : not reported
CredibleMeds (4) : not reported
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'
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IC index = (AFKr/((AFNaL+AFCaL)/2))*100
where
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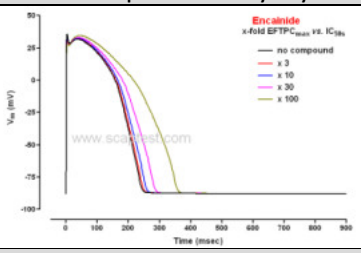
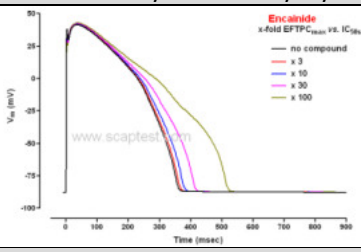
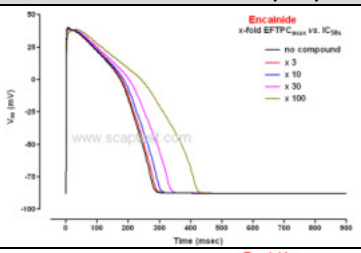
Human epicardial myocytes



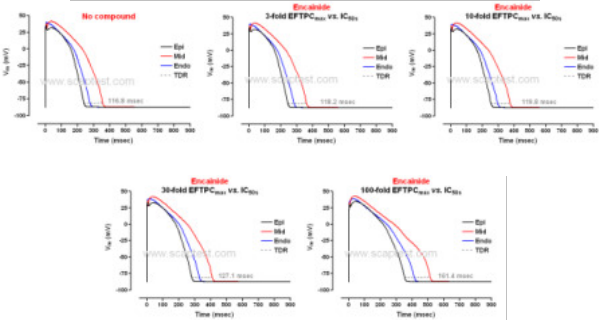
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarisation



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1 - CL 1000 msec without compound
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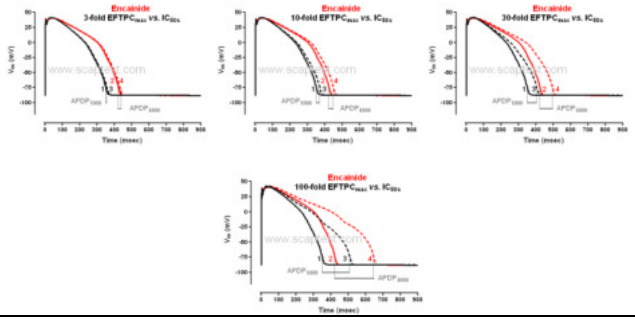
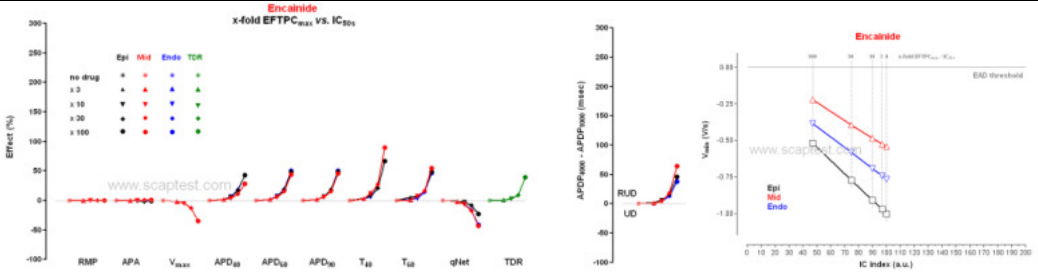


Summary



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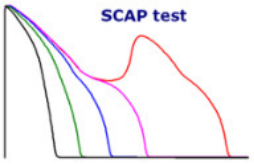

Drug

Erythromycin

Macrolide antibiotic used to treat various bacterial infections
no longer marketed in France, Singapore, Greece, Denmark and Sweden (Onakpoya et al (2016) *BMC Med.* **14**: 10)

Raw data

IC_{50s} (slope) (1)

I_{CaL} : ---- µM (---)
I_{Kr} : 38.9 µM (1.0)
I_{Na} : ---- µM (---)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ (1)

8.516 µM

TdP risk

Redfern (2) : numerous TdP reports (class 3)
Kramer (3) : not reported
CredibleMeds (4) : known risk of TdP (class 1)
CiPA (5) : not reported
WP (6) : 8/1 (TdP+/TdP-)

Results

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Simulation conditions:

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where
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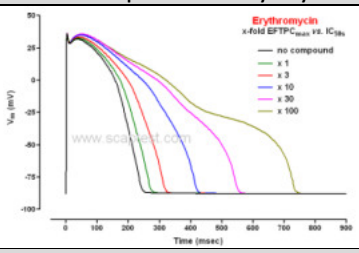
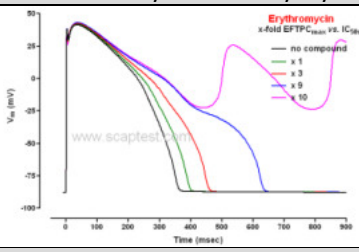
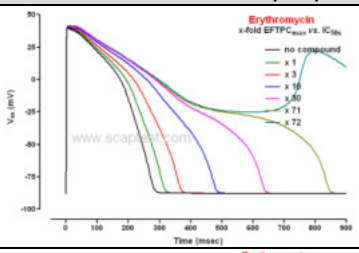
Human epicardial myocytes



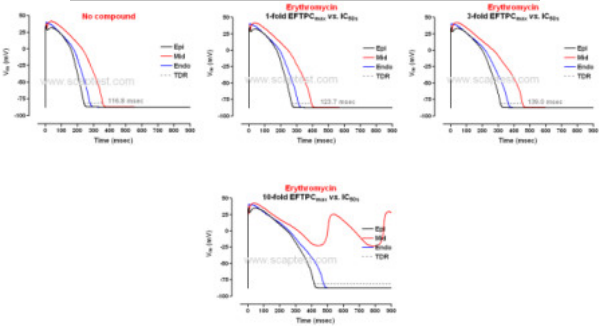
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarisation



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1 - CL 1000 msec without compound
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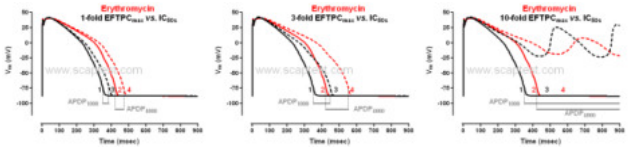
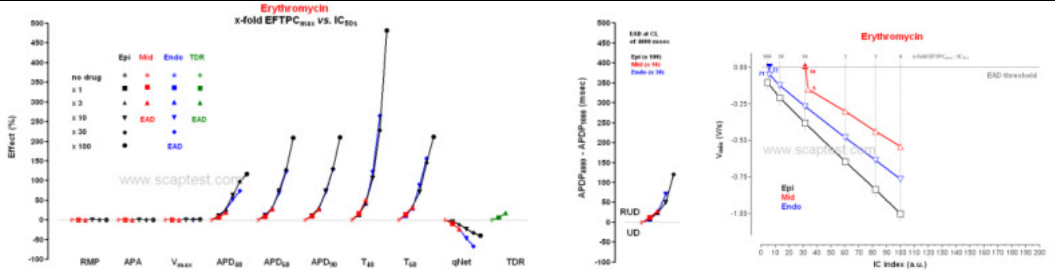


Summary



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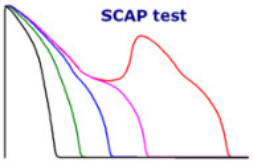
2. Redfern WS et al. (2003) *Cardiovasc. Res.* **58**: 32-45
3. Kramer J et al. (2013) *Sci.rep.* **3** : 2100
4. Woosley RL (2015) www.CredibleMeds.org
5. CiPA (2016) www.ilsiextra.org/hesi/science/cardiac/cipa/Project
6. Wiśniowska B et al. (2017) *Drug discovery today* **22** : 10-16
7. O'Hara T et 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

Etravirine

Non-nucleoside reverse transcriptase inhibitor used to treat HIV-1 infections

Raw data

IC_{50s} (slope) [1]

I_{CaL} : --- µM (---)
I_{Kr} : 158.49 µM (1.0)
I_{Na} : 501.19 µM (1.0)
I_{Ks} : 1258.9 µM (1.0)
I_{to} : 3162.3 µM (1.0)
I_{NaL} : --- µM (---)
I_{K1} : --- µM (---)

$EFTPC_{max}$ [1]

0.00258 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
- 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:

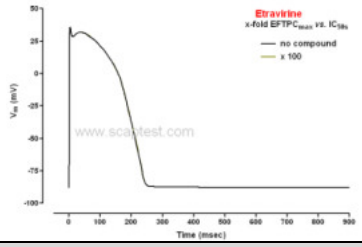
- TDR = APD_{90} mid - APD_{90} epi (at CL of 1000 msec)
- RUD = $APD_{90}P_{4000}$-$APD_{90}P_{1000}$

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

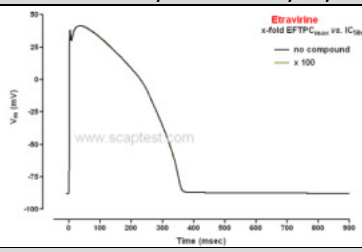
IC index calculation [9]:

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

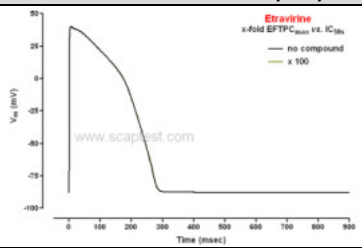
Human epicardial myocytes



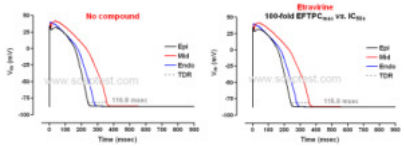
Human midmyocardial myocytes



Human endocardial myocytes

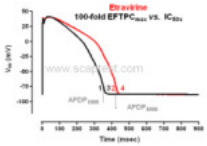


Transmural dispersion of repolarisation

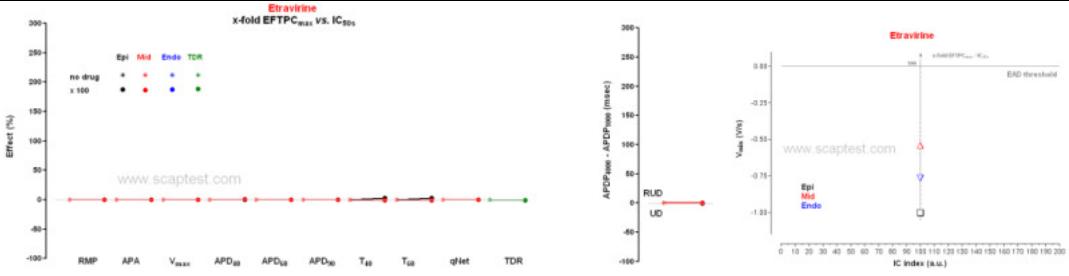


Reverse use dependence on midmyocardial myocytes

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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Abbreviations

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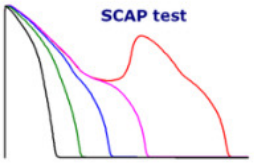

Drug

Everolimus

Mammalian target of rapamycin (mTOR) kinase inhibitor used to treat various types of malignancies

Raw data

IC_{50s} (slope) [1]

I_{CaL} : --- µM (---)
I_{Kr} : 501.187 µM (1.0)
I_{Na} : 630.957 µM (1.0)
I_{Ks} : 100.00 µM (1.0)
I_{to} : 10000.0 µM (1.0)
I_{NaL} : --- µM (---)
I_{K1} : --- µM (---)

$EFTPC_{max}$ [1]

0.068105 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
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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}

$$I_j = g\,O(V - E_{ion})$$

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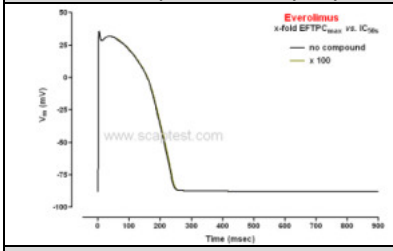
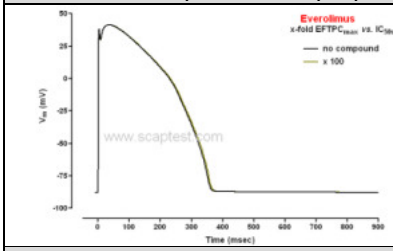
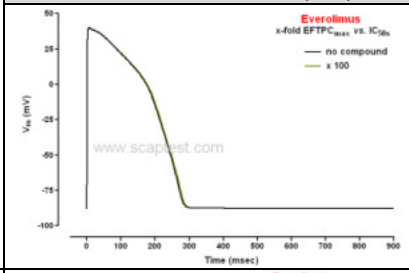
Human epicardial myocytes



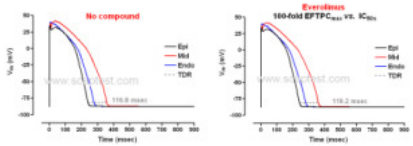
Human midmyocardial myocytes



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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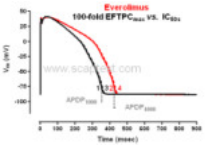
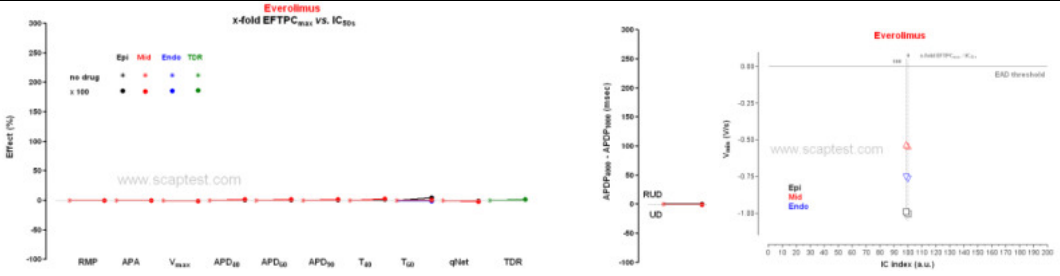


Summary



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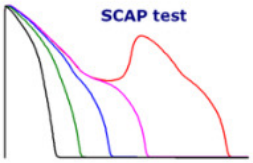

Drug

Famotidine

Histamine H_2 receptor antagonist used to treat duodenal ulcers, begnin gastric ulcers or gastroesophageal reflux disease

Raw data

IC_{50s} (slope) [1]

I_{CaL} : ---- µM (---)
I_{to} : ---- µM (---)
I_{Kr} : 2325.3 µM (1.0)
I_{NaL} : ---- µM (---)
I_{Na} : ---- µM (---)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ [1]

0.33 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] : 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)

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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
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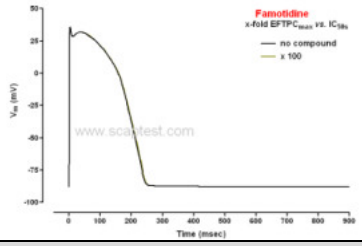
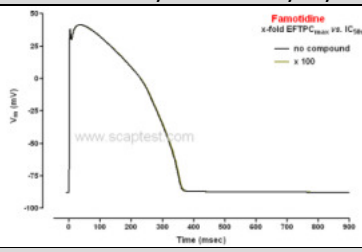
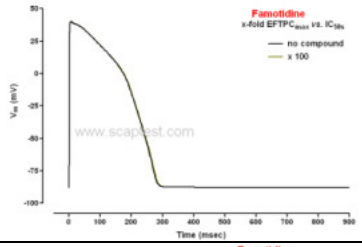
Human epicardial myocytes



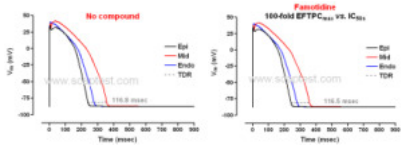
Human midmyocardial myocytes



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
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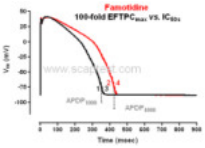
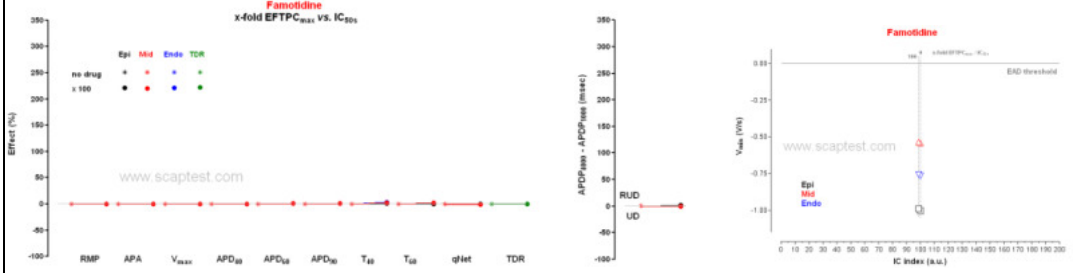


Summary



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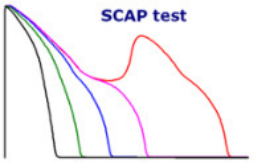

Drug

Fexofenadine

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

Raw data

IC_{50s} (slope) [1]

I_{CaL} : ---- µM (---)
I_{Kr} : 501.0 µM (1.0)
I_{Na} : ---- µM (---)
I_{Ks} : 20.4 µM (1.0)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ [1]

0.345 µM

TdP risk

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

Results

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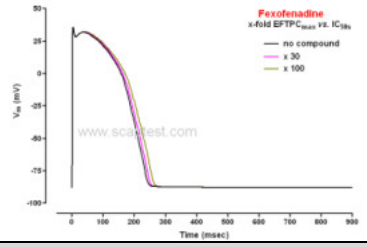
$I_j = g\,O\,(V - E_{ion})$ (g = maximal conductance of channel j; O = open probability of channel j; V = voltage membrane; E_{ion} = reversal potential for species of ions which flows through channel j)

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

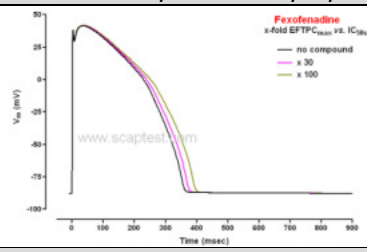
TDR and RUD estimation:
- TDR = APD_{90} mid - APD_{90} epi (at CL of 1000 msec)
- RUD = $APD_{90}P_{4000}$-$APD_{90}P_{1000}$ where $APD_{90}P_x$ = APD_{90} with - APD_{90} without compound at CL x

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}

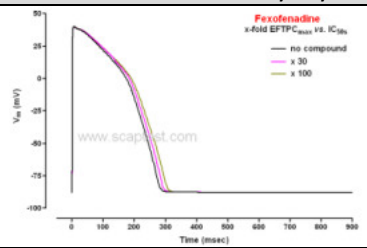
Human epicardial myocytes



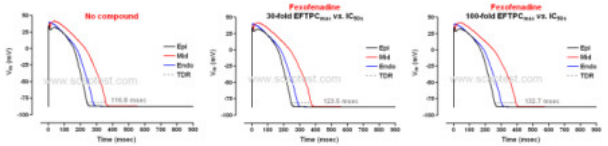
Human midmyocardial myocytes



Human endocardial myocytes

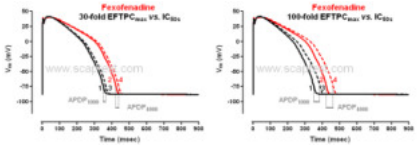


Transmural dispersion of repolarisation

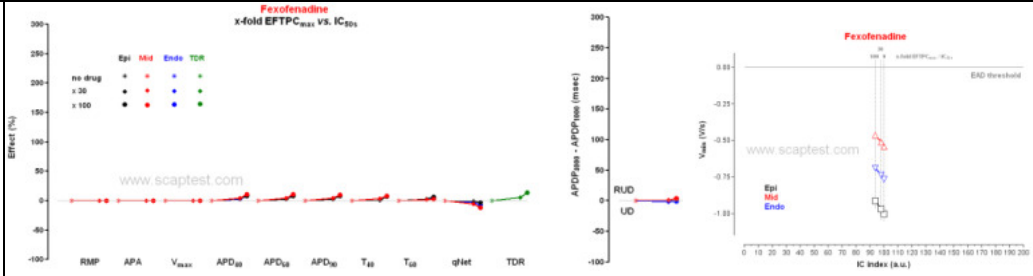


Reverse use dependence on midmyocardial myocytes

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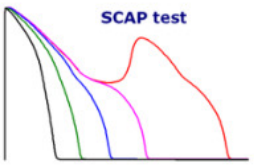
Abbreviations

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_{to}+I_{Na}+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

Flecainide

Multichannel blocker used as Class IC antiarrhythmic to treat atrial fibrillation and paroxysmal supraventricular tachycardia

Raw data

IC_{50s} (slope) (1)

I_{CaL} : 27.1 µM (0.97)
I_{to} : ---- µM (---)
I_{Kr} : 1.5 µM (0.88)
I_{NaL} : ---- µM (---)
I_{Na} : 6.2 µM (1.14)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ (1)

0.753 µM

TdP risk

Redfern (2) : numerous reports of TdP (class 3)
Kramer (3) : torsadogenic (class 2)
CredibleMeds (4) : known risk of TdP (class 1)
CiPA (5) : not reported
WP (6) : 8/1 (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}

$$I_j = g\,O(V - E_{ion})$$

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'

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

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

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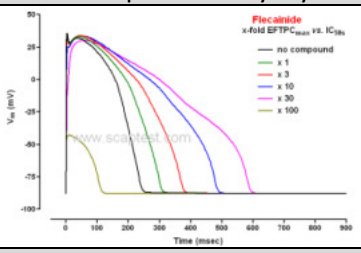
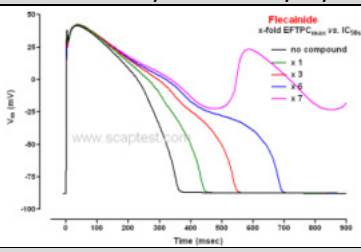
IC index = (AFKr/((AFNaL+AFCaL)/2))*100
where
AFKr, AFNaL and AFCaL = active fraction (%) of the I_{Kr}, I_{NaL} and I_{CaL}

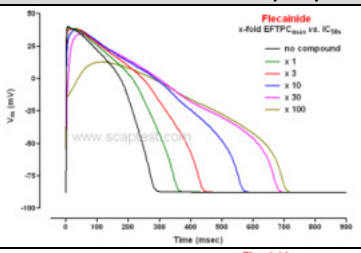
Human epicardial myocytes



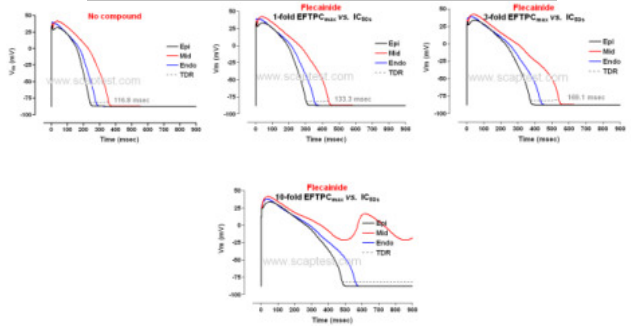
Human midmyocardial myocytes



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
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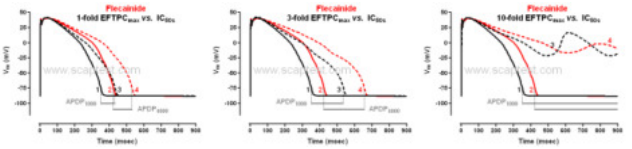
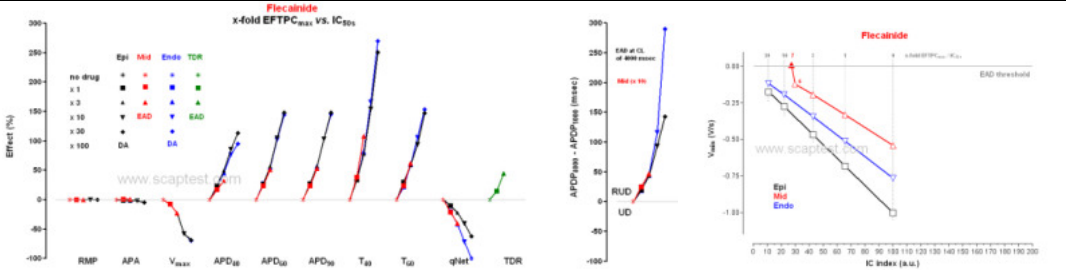
4 - CL 4000 msec with compound



Summary



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Abbreviations

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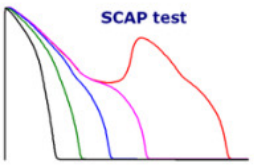

Drug

Fluoxetine

5-HT reuptake inhibitor used to treat bulimia, major depressive, obsessive compulsive premenstrual dysphoric, panic and bipolar disorders

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 2.82 µM (1.0)
I_{to} : ---- µM (---)
I_{Kr} : 1.5µM (1.0)
I_{NaL} : ---- µM (---)
I_{Na} : 39.4 µM (1.0)
I_{K1} : ---- µM (---)
I_{Ks}: ---- µM (---)

$EFTPC_{max}$ [1]

0.011 µM

TdP risk

Redfern [2] : isolated reports of TdP (class 4)
Kramer [3] : not reported
CredibleMeds [4] : conditional risk of TdP (class 3)
CiPA [5] : not reported
WP [6] : 3/2 (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'
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IC index = (AFKr/((AFNaL+AFCaL)/2))*100
where
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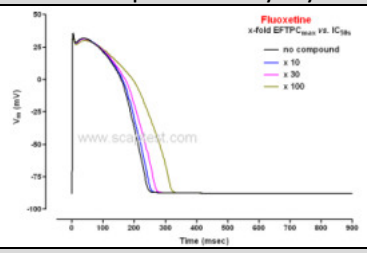
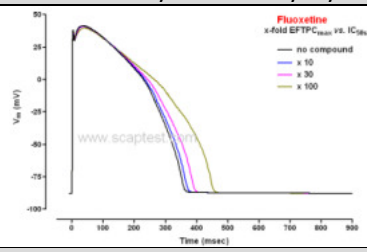
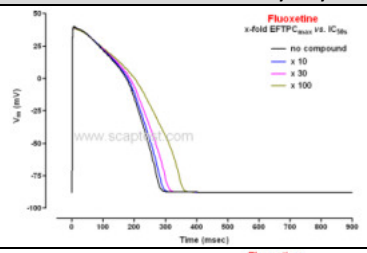
Human epicardial myocytes



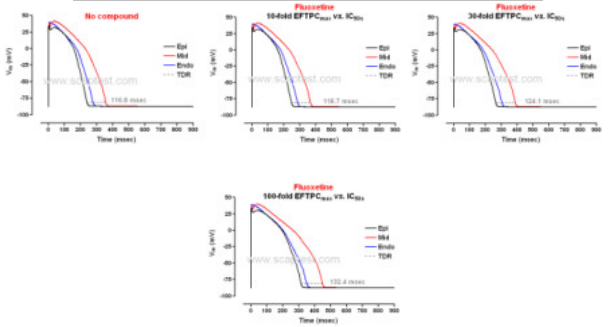
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarisation



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1 - CL 1000 msec without compound
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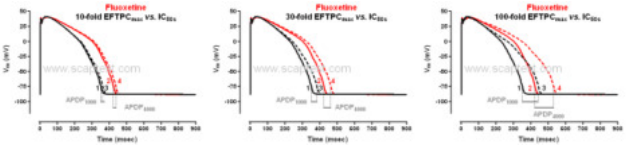

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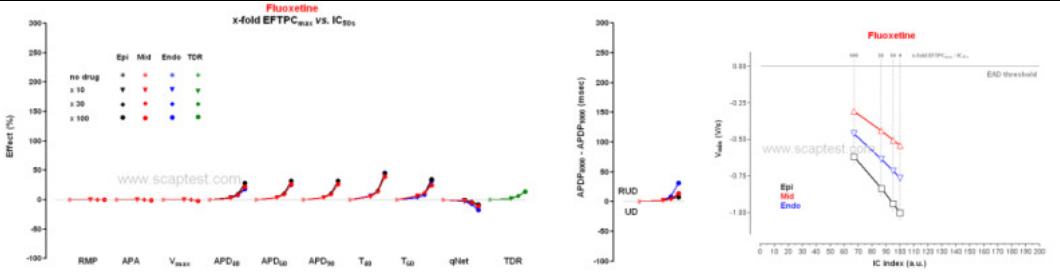

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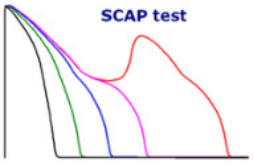

Drug

Fluvoxamine

5-HT reuptake inhibitor used to treat obsessive compulsive disorder
no longer marketed in Iceland (Onakpoya et al (2016) *BMC Med.* **14**: 10))

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 4.90 µM (1.0)
I_{Kr} : 3.80 µM (1.0)
I_{Na} : 39.36 µM (1.0)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ [1]

0.264 µM

TdP risk

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Kramer [3] : not reported
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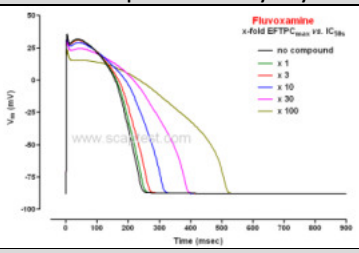
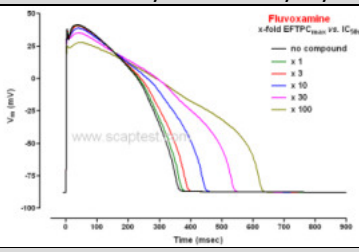
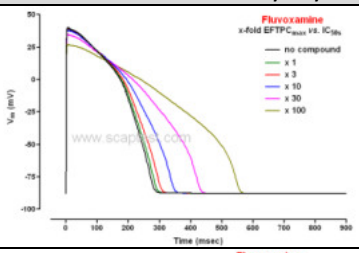


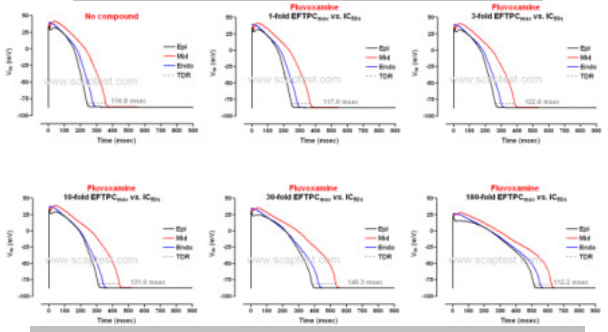
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarisation



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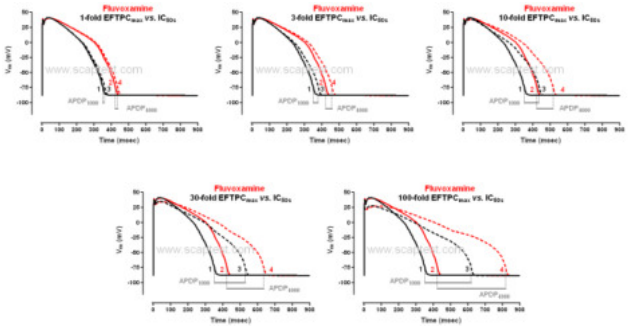
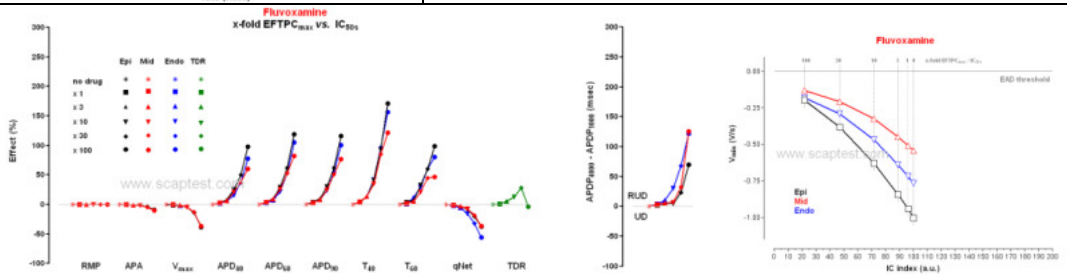


Summary



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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

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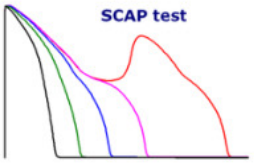


Drug

Gatifloxacin

Fluoroquinolone antibiotic used to treat a wide variety of bacterial infections
no longer marketed in Europe and India (Onakpoya et al (2016) *BMC Med.* **14**: 10)

Raw data

IC_{50s} (slope) [1]

I_{CaL} : ---- µM (---)
I_{Kr} : 25.4 µM (1.0)
I_{Na} : ---- µM (---)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ [1]

9.0 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] : 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'

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

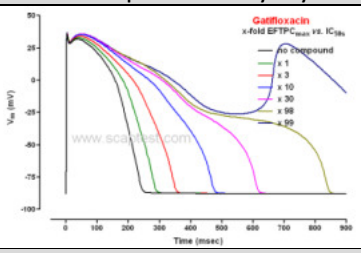
g = maximal conductance of channel 'j'
$g_{control\_j}$ = drug-free maximal conductance of channel 'j'
IC50 = 50% of inhibition of a drug for channel 'j'
D= drug concentration (EFTPC for example)
n= hill slope

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

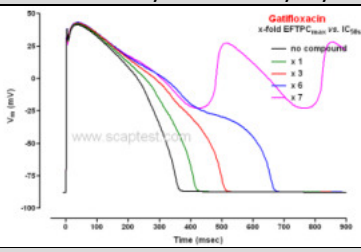
where
$APD_{90}P_x$ = APD_{90} with - APD_{90} without compound at CL x

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}

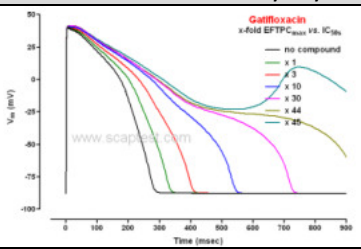
Human epicardial myocytes



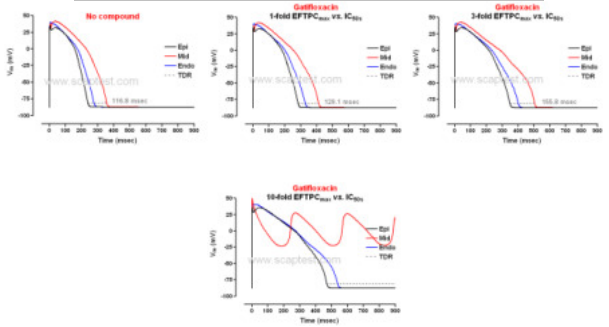
Human midmyocardial myocytes



Human endocardial myocytes

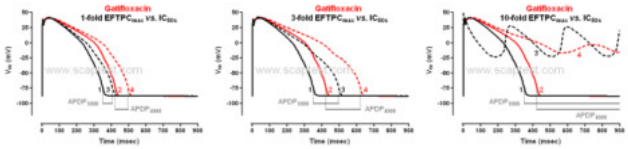


Transmural dispersion of repolarisation

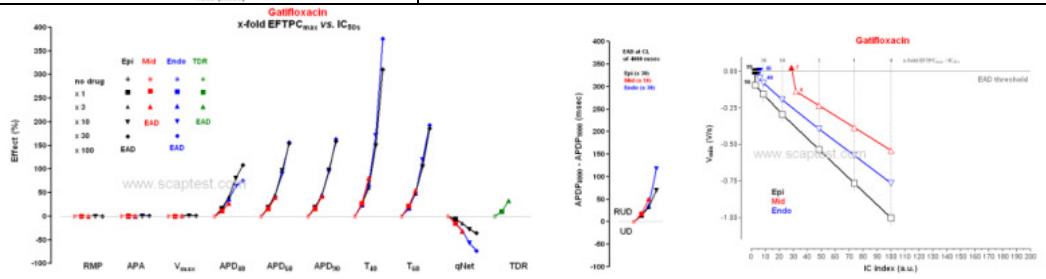


Reverse use dependence on midmyocardial myocytes

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
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Abbreviations

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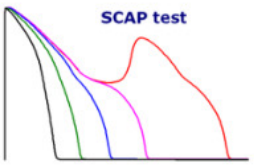

Drug

Gefitinib

Tyrosine kinase inhibitor used to treat non-small cell lung carcinoma

Raw data

IC_{50s} (slope) (1)

I_{CaL} : ---- µM (---)
I_{to} : ---- µM (---)
I_{Kr} : 1.10 µM (1.0)
I_{NaL} : ---- µM (---)
I_{Na} : ---- µM (---)
I_{K1} : ---- µM (---)
I_{Ks} : 23.8 µM (1.7)

$EFTPC_{max}$ (1)

0.0913 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}

$$I_j = g\,O(V - E_{ion})$$

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
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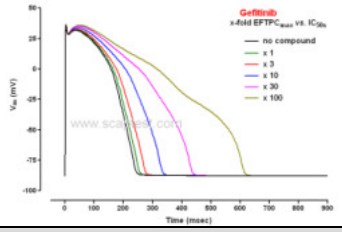
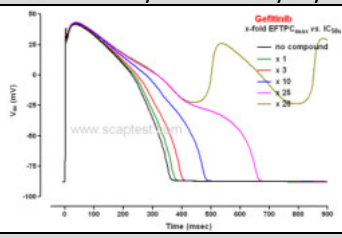
IC index calculation (9):

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

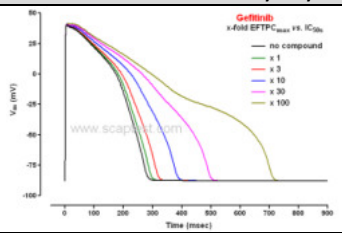
Human epicardial myocytes



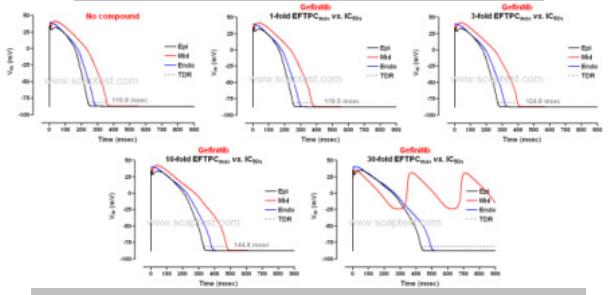
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarisation



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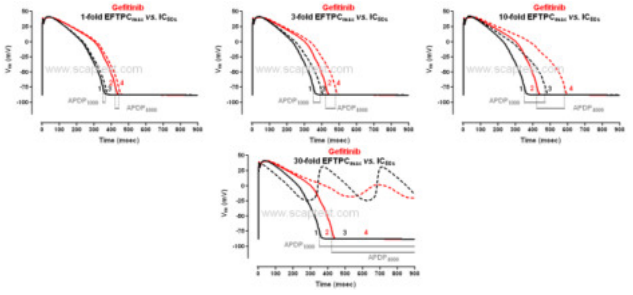
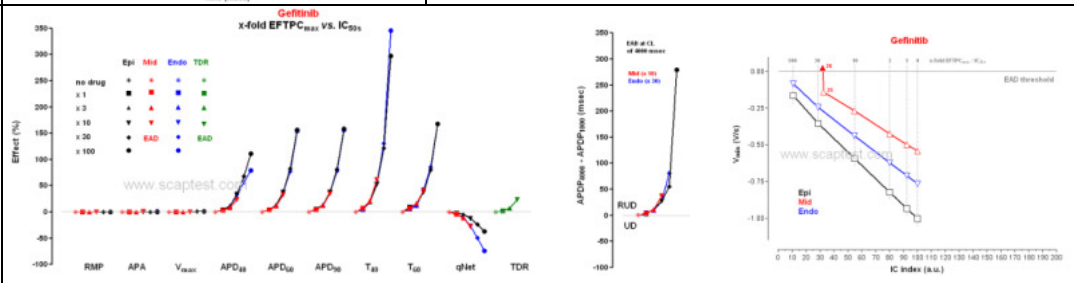


Summary



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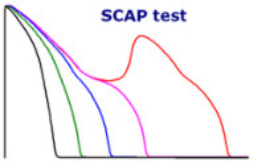

Drug

Halofantrine

Ferriprotophorphyrin IX complexing agent used to treat malaria

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 1.9 µM (0.99)
I_{to} : ---- µM (---)
I_{Kr} : 0.38 µM (1.31)
I_{NaL} : ---- µM (---)
I_{Na} : 331.2 µM (1.0)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ [1]

0.172 µM

TdP risk

Redfern [2] : numerous reports of TdP (class 3)
Kramer [3] : torsadogenic (class 2)
CredibleMeds [4] : known risk of TdP (class 1)
CiPA [5] : not reported
WP [6] : 9/0 (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):
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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'

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IC50 = 50% of inhibition of a drug for channel 'j'
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where
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IC index = (AFKr/((AFNaL+AFCaL)/2))*100
where
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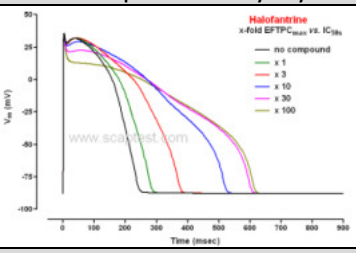
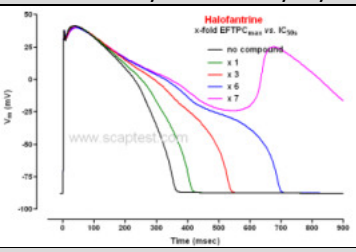
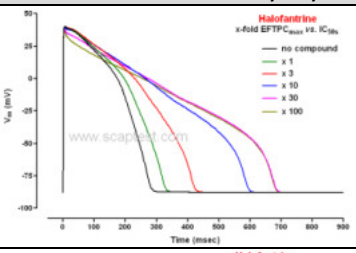
Human epicardial myocytes



Human midmyocardial myocytes



Human endocardial myocytes



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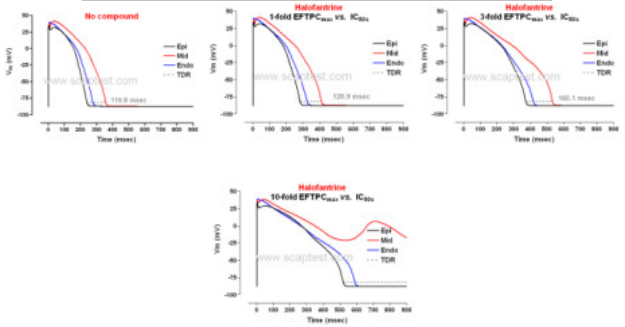

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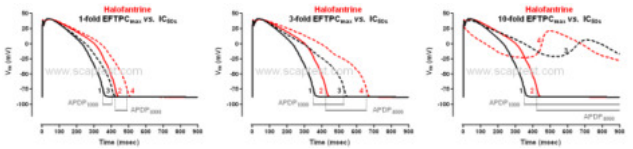
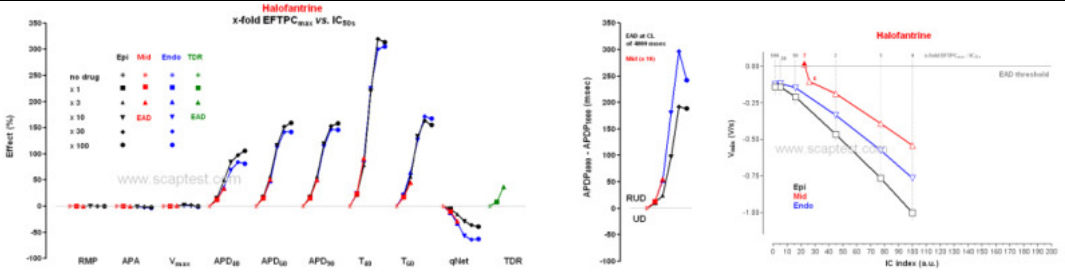


Summary



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2. Redfern WS et al. (2003) *Cardiovasc. Res.* **58** : 32-45
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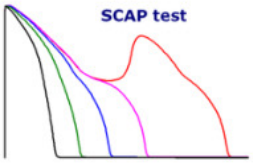


Drug

Haloperidol

Dopamine D_2 receptor antagonist used to treat schizophrenia and other psychoses

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 1.3 µM (1.38)
I_{Kr} : 0.04 µM (1.18)
I_{Na} : 4.3 µM (1.58)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ [1]

0.004 µM

TdP risk

Redfern [2] : numerous reports of TdP (class 3)
Kramer [3] : torsadogenic (class 2)
CredibleMeds [4] : known risk of TdP (class 1)
CiPA [5] : not reported
WP [6] : 11/0 (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

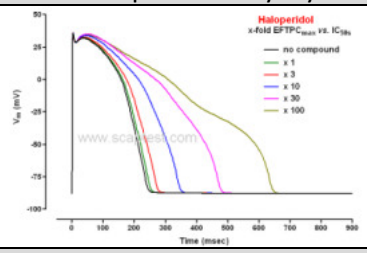
TDR and RUD estimation:

- TDR = APD_{90} mid - APD_{90} epi (at CL of 1000 msec)
- RUD = $APD_{90}P_{4000}$-$APD_{90}P_{1000}$
  where
  $APD_{90}P_x$ = APD_{90} with - APD_{90} without compound at CL x

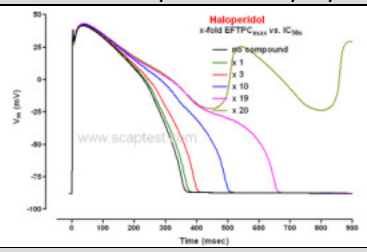
IC index calculation [9]:

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

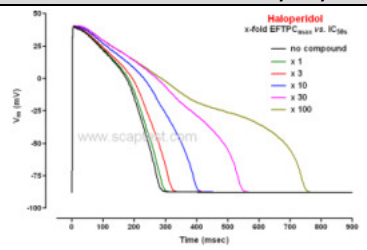
Human epicardial myocytes



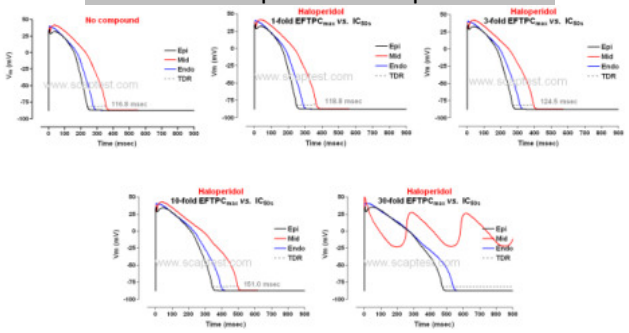
Human midmyocardial myocytes



Human endocardial myocytes

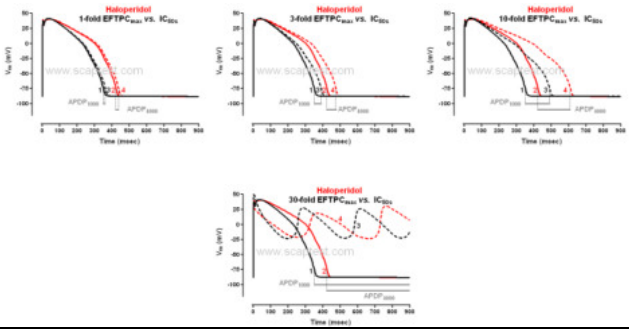


Transmural dispersion of repolarisation

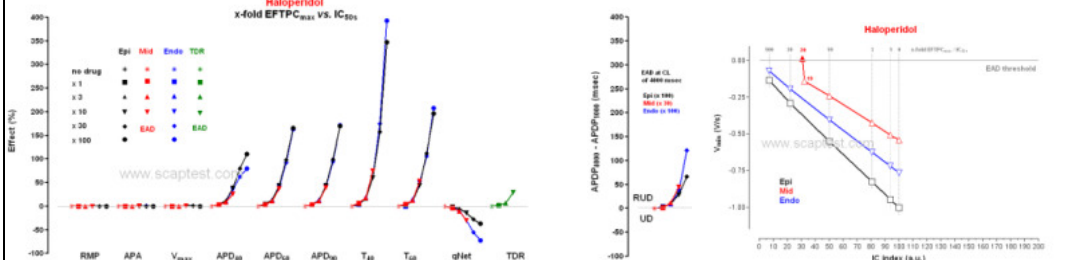


Reverse use dependence on midmyocardial myocytes

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

Abbreviations

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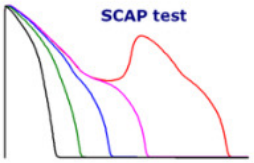

Drug

Hydroxychloroquine

Ferriprotophorphyrin IX complexing agent used to treat malaria

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 26.9 µM (1.0)
I_{Kr} : 5.62 µM (1.0)
I_{Na} : ---- µM (---)
I_{Ks} : 9.33 µM (1.0)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ [1]

1.22 µM

TdP risk

Redfern [2] : not reported
Kramer [3] : not reported
CredibleMeds [4] : known TdP risk (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; V= voltage membrane; E_{ion} = reversal potential for species of ions which flows through channel j

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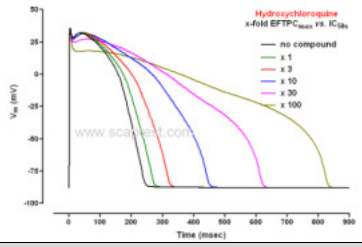
- TDR = APD_{90} mid - APD_{90} epi (at CL of 1000 msec)
- RUD = $APD_{90}P_{x1000}$-$APD_{90}P_{1000}$

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

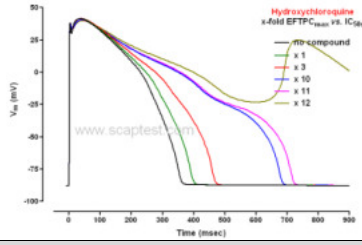
IC index calculation [9]:

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

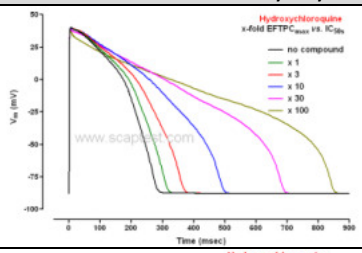
Human epicardial myocytes



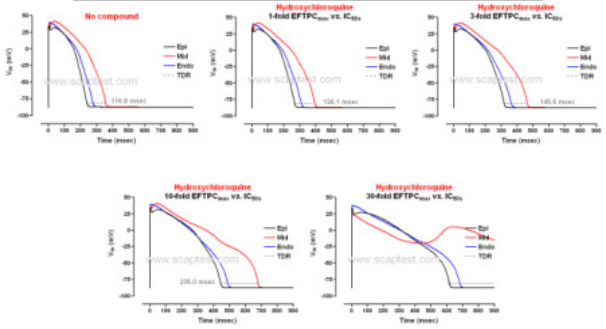
Human midmyocardial myocytes



Human endocardial myocytes

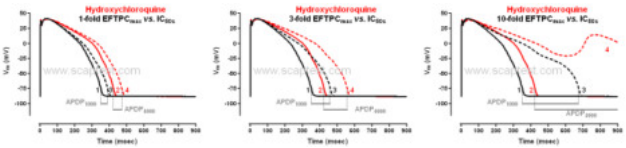


Transmural dispersion of repolarisation

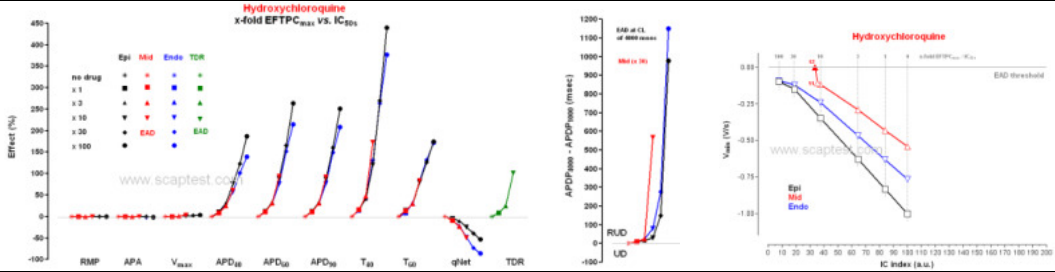


Reverse use dependence on midmyocardial myocytes

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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Abbreviations

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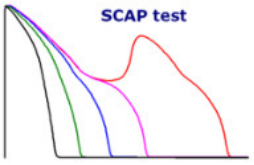

Drug

Hydroxyzine

Histmaine H_1 receptor antagonist used to treat anxiety, pruritus or chronic urticaria

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 8.6 µM (1.0)
I_{to} : 10.1 µM (1.0)
I_{Kr} : 0.39 µM (1.0)
I_{NaL} : 5.8 µM (1.0)
I_{Na} : 0.3 µM (1.0)
I_{K1} : >30 µM (---)
I_{Ks} : >30 µM (---)

$EFTPC_{max}$ [1]

0.01 µM

TdP risk

Redfern [2] : no published report of TdP (class 5)
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}

$I_j = g\,O\,(V - E_{ion})$

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'

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

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IC50 = 50% of inhibition of a drug for channel 'j'
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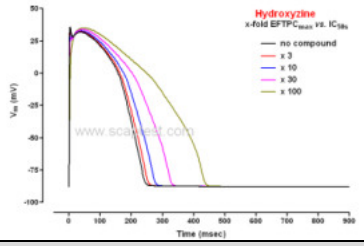
- TDR = APD_{90} mid - APD_{90} epi (at CL of 1000 msec)
- RUD = $APD_{90}P_{4000}$- $APD_{90}P_{1000}$

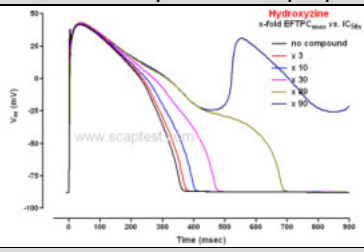
where
$APD_{90}P_x$ = APD_{90} with - APD_{90} without compound at CL x

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}.

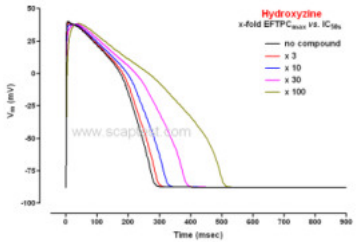
Human epicardial myocytes



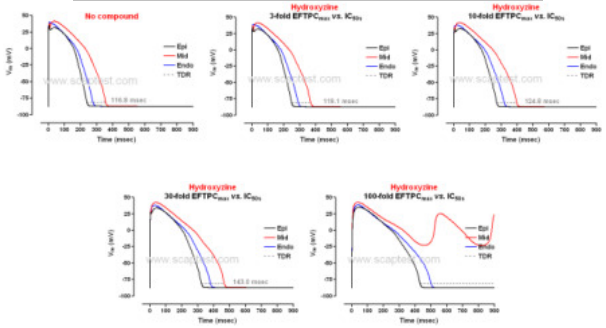
Human midmyocardial myocytes



Human endocardial myocytes

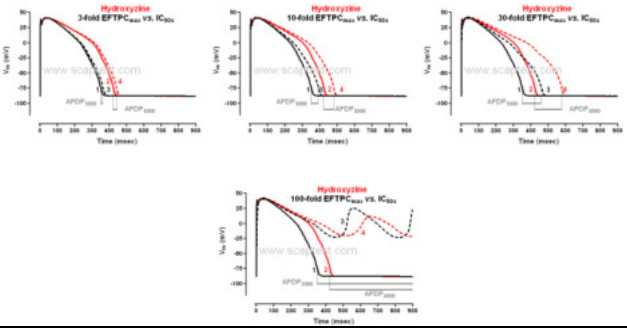


Transmural dispersion of repolarisation

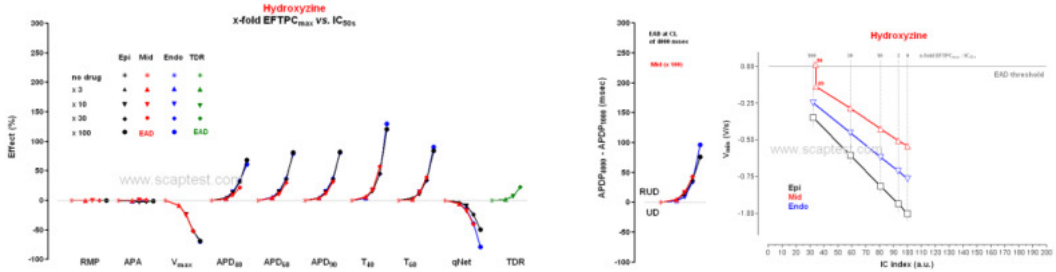


Reverse use dependence on midmyocardial myocytes

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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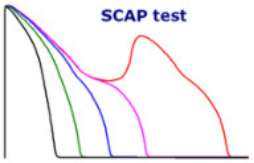

Drug

Ibutilide

Multichannel inhibitor used as Class III antiarrhythmic to treat atrial fibrillation and atrial flutter

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 62.5 µM (1.16)
I_{to} : ---- µM (---)
I_{Kr} : 0.018 µM (1.53)
I_{NaL} : ---- µM (---)
I_{Na} : 42.5 µM (1.03)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ [1]

0.14 µM

TdP risk

Redfern [2] : class IA or III antiarrhythmics (class 1)
Kramer [3] : torsadogenic (class 2)
CredibleMeds [4] : known risk of TdP (class 1)
CiPA [5] : high risk of TdP (class 1)
WP [6] : 11/0 (TdP+/TdP-)

Results

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

Simulation conditions:
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$I_j = g_j O(V - E_{ion})$ (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_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)

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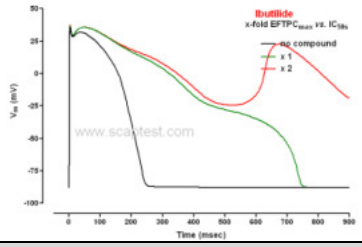
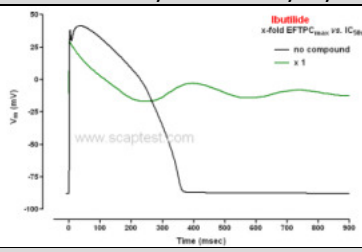
IC index = (AFKr/((AFNaL+AFCaL)/2))*100
where
AFKr, AFNaL and AFCaL = active fraction (%) of the I_{Kr}, I_{NaL} and I_{CaL}

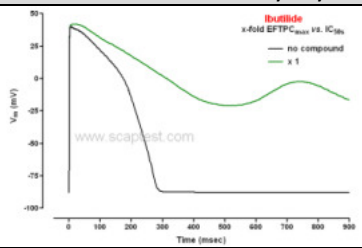
Human epicardial myocytes



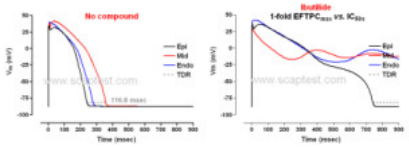
Human midmyocardial myocytes



Human endocardial myocytes

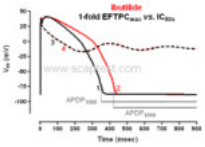


Transmural dispersion of repolarisation



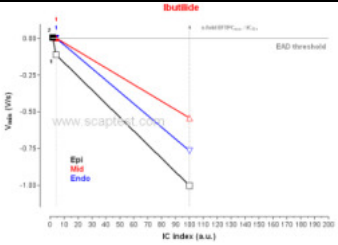
Reverse use dependence on midmyocardial myocytes

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

EAD at 1-fold $EFTPC_{max}$ *vs.* IC_{50s} on midmyocardial and endocardial myocytes



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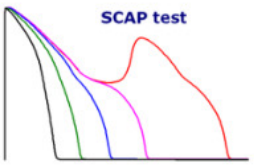
Abbreviations

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

Imipramine

5-HT and noradrenaline reuptake inhibitor used to treat depression and childhood enuresis

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 8.1 µM (1.0)
I_{to} : 50.0 µM (1.0)
I_{Kr} : 3.4 µM (1.0)
I_{NaL} : 0.0 µM (---)
I_{Na} : 3.6 µM (1.0)
I_{K1} : 0.0 µM (---)
I_{Ks} : 0.0 µM (---)

$EFTPC_{max}$ [1]

0.106 µM

TdP risk

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

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

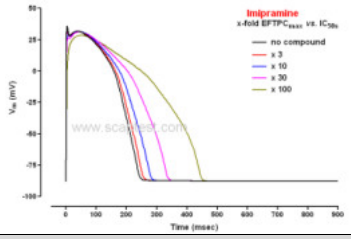
TDR and RUD estimation:

- TDR = APD_{90} mid - APD_{90} epi (at CL of 1000 msec)
- RUD = $APD_{90}P_{x000}$-$APD_{90}P_{1000}$ where $APD_{90}P_x$ = APD_{90} with - APD_{90} without compound at CL x

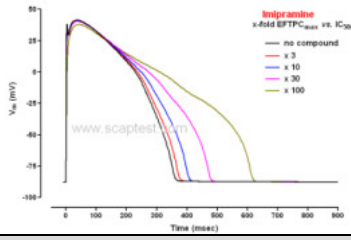
IC index calculation [9]:

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

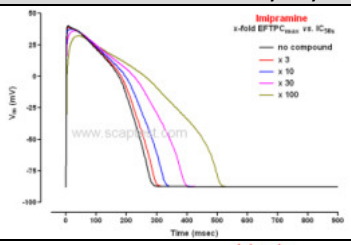
Human epicardial myocytes



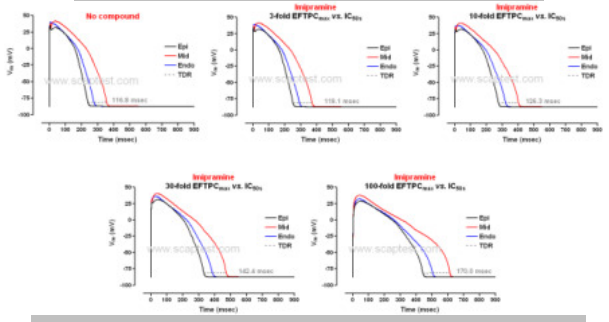
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarisation



Reverse use dependence on midmyocardial myocytes

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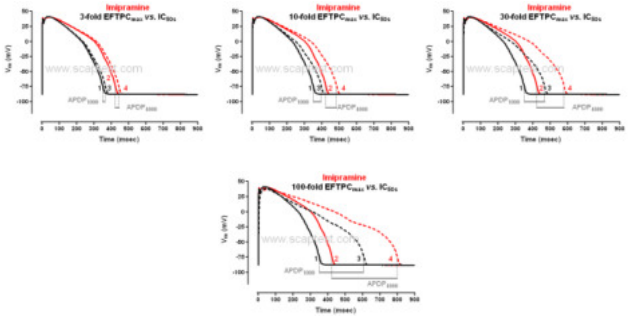
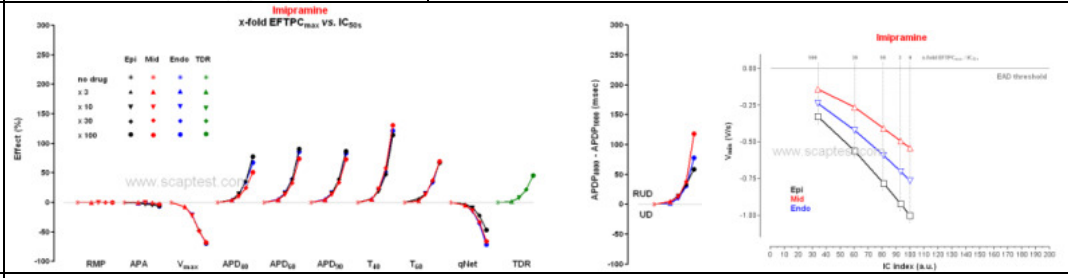


Summary



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Abbreviations

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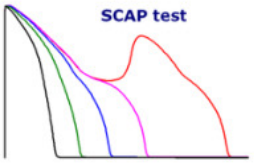

Drug

Ivabradine

Hyperpolarisation-activated, cyclic nucleotide-gated cation channels (HCN1-4) blocker used to treat stable symptomatic heart failure

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 34.09 µM (1.00)
I_{to} : ---- µM (---)
I_{Kr} : 3.6 µM (0.99)
I_{NaL} : ---- µM (---)
I_{Na} : 78.947 µM (1.00)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ [1]

0.014 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] : 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 = 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)

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where
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IC index calculation [9]:
IC index = (AFKr/((AFNaL+AFCaL)/2))*100
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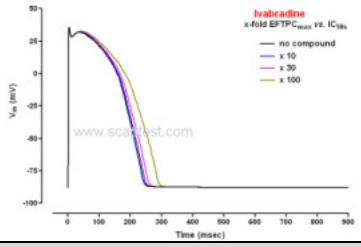
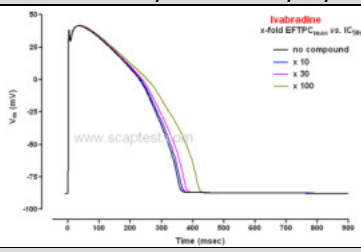
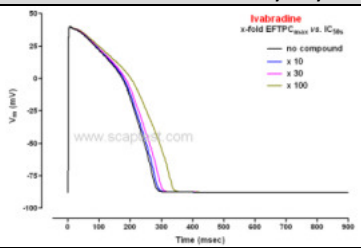
Human epicardial myocytes



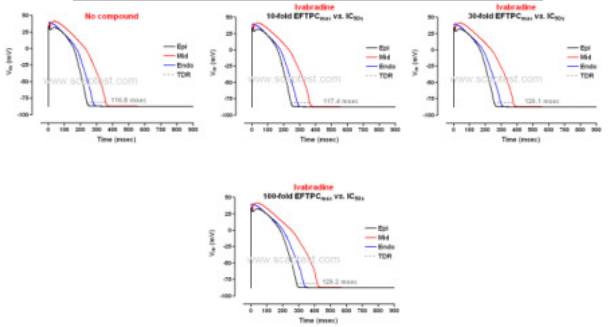
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarisation



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1 - CL 1000 msec without compound
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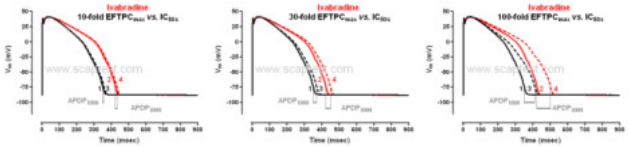
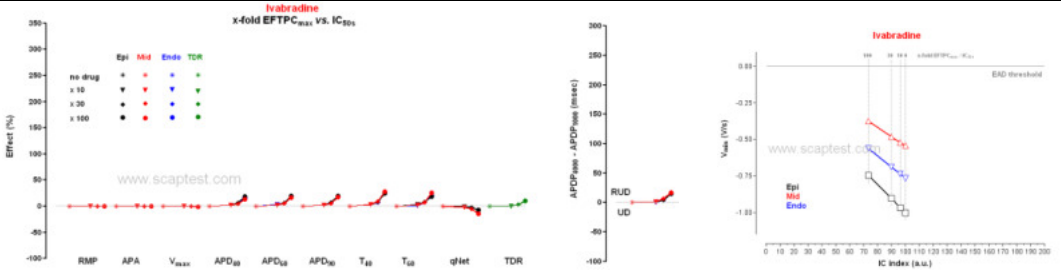


Summary



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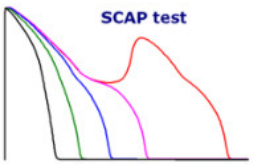

Drug

Ketanserin

Serotonin 5-HT$_{2A}$ receptor inverse agonist investigated to treat septic shock, severe septis and diabetic foot ulcer

Raw data

IC$_{50s}$ (slope) [1]

I_{CaL} : ---- µM (---)
I_{Kr} : 0.75 µM (1.24)
I_{Na} : ---- µM (---)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

EFTPC$_{max}$ [1]

0.018 µM

TdP risk

Redfern [2] : isolated TdP reports (class 4)
Kramer [3] : not reported
CredibleMeds [4] : possible risk of TdP (class 2)
CiPA [5] : not reported
WP [6] : 3/2 (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
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where
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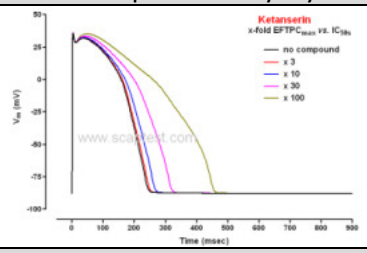
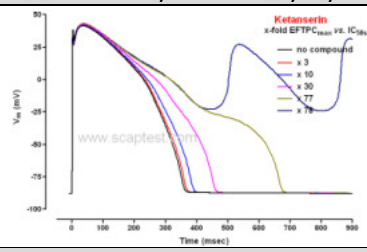
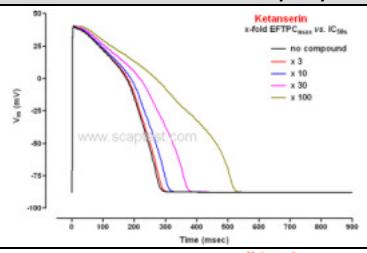
Human epicardial myocytes



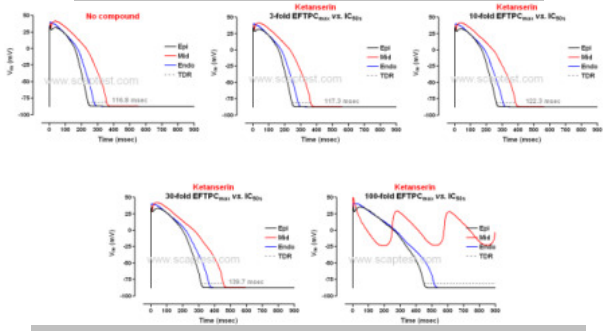
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarisation



Reverse use dependence on midmyocardial myocytes

1 - CL 1000 msec without compound
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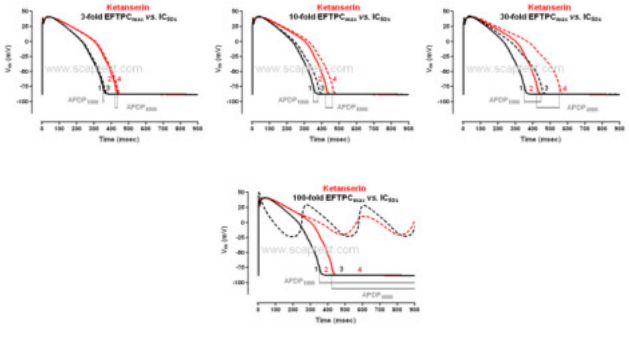
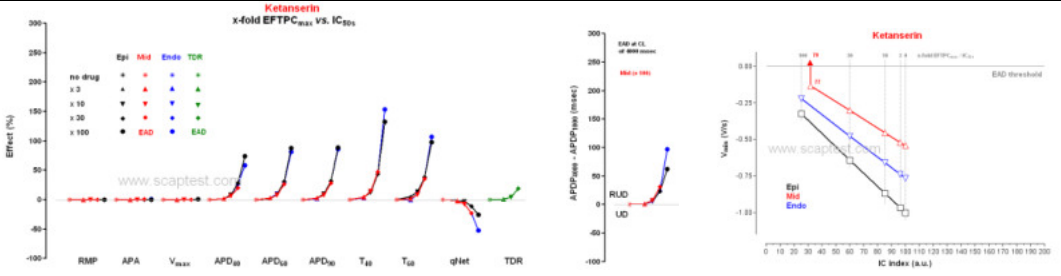


Summary



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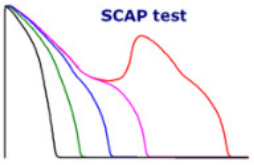
Abbreviations

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_{to}+I_{Na}+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

Ketoconazole

14-α-sterol demethylase inhibitor used to treat seborrheic dermatitis and fungal skin infections
no longer marketed in Europe and Australia (Onakpoya et al (2016) *BMC Med.* **14**: 10)

Raw data

IC_{50s} (slope) [1]

I_{CaL} : ---- µM (---)
I_{Kr} : 4.61 µM (1.53)
I_{Na} : 44.9 µM (1.0)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ [1]

0.177 µM

TdP risk

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

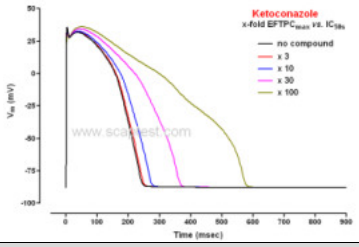
$g_j = g_{control,j}\left[1 + \left(\frac{D}{IC50_j}\right)^n\right]^{-1}$ (g = maximal conductance of channel 'j', $g_{control,j}$ = drug-free maximal conductance of channel 'j', IC50 = 50% of inhibition of a drug for channel 'j', D= drug concentration (EFTPC for example), n= hill slope)

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

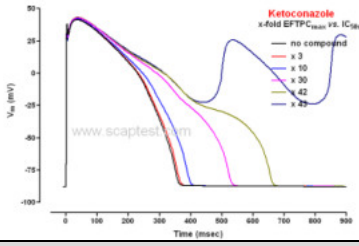
where
$APD_{90}P_x$ = APD_{90} with - APD_{90} without compound at CL x

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}

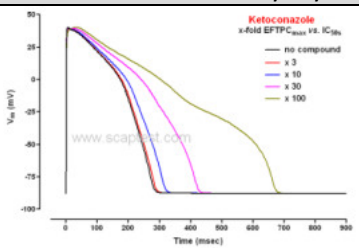
Human epicardial myocytes



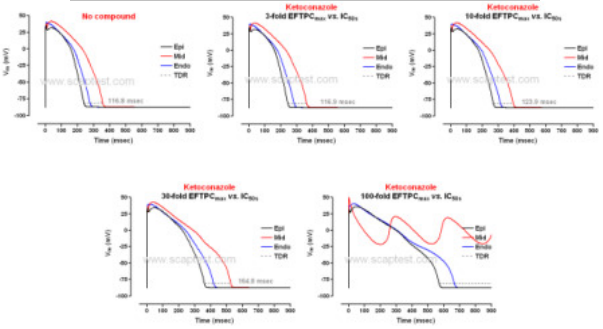
Human midmyocardial myocytes



Human endocardial myocytes

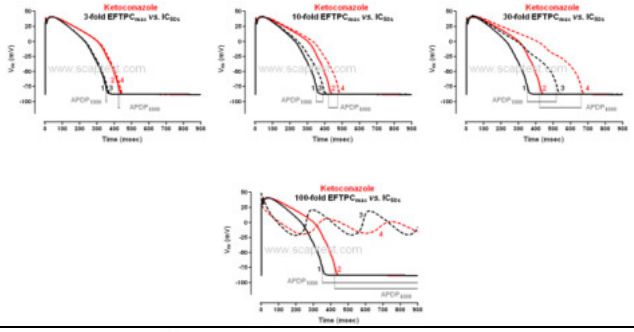


Transmural dispersion of repolarisation

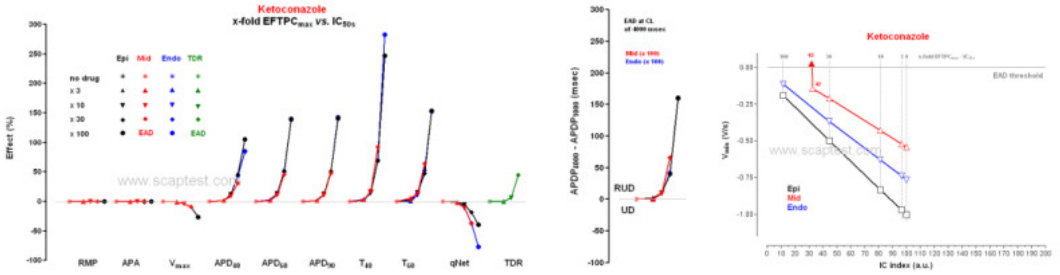


Reverse use dependence on midmyocardial myocytes

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. Wiśniowska B et al. (2017) *Drug discovery today* **22**: 10-16
7. O'Hara T et al. (2011) *PLoS Comput. Biol.* **7**: e1002061.8
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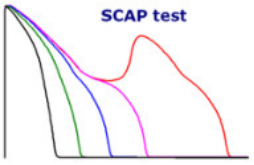

Drug

Lacosamide

Voltage-gated Na^+ channel ($Na_v1.5$) bloker used to treat partial onset seizure in epilepsy

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 50.12 µM (1.0)
I_{Kr} : 50118.72 µM (1.0)
I_{Na} : 501.19 µM (1.0)
I_{Ks} : 251.19 µM (1.0)
I_{to} : --- µM (---)
I_{NaL} : --- µM (---)
I_{K1} : --- µM (---)

$EFTPC_{max}$ [1]

60.46 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}

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where
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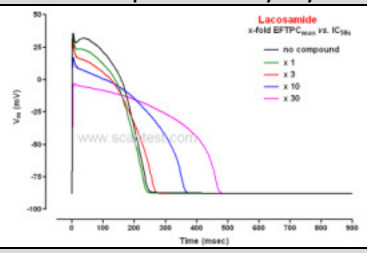
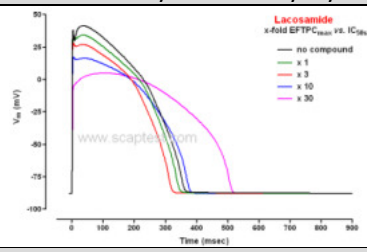
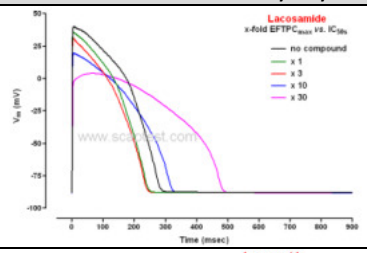
Human epicardial myocytes



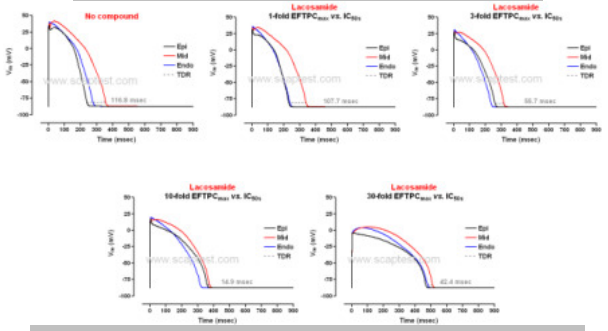
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarisation



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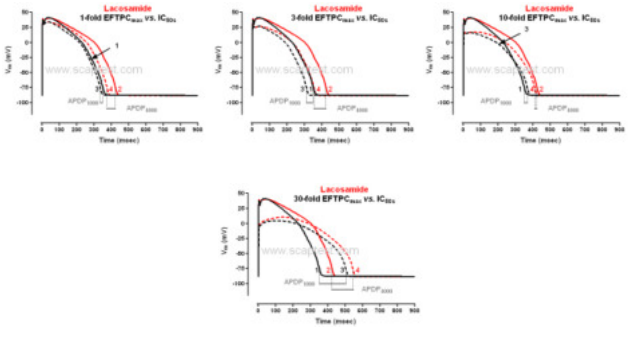

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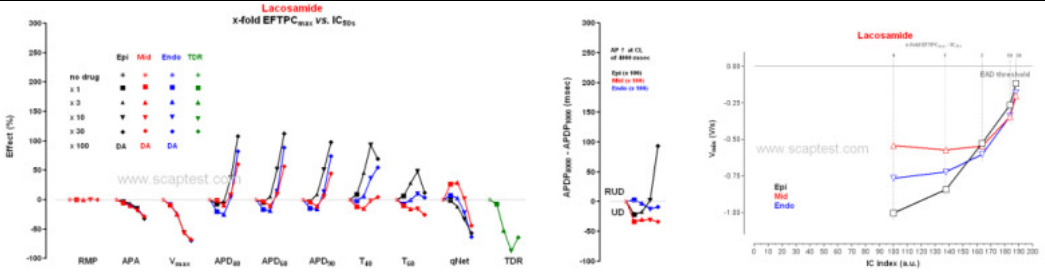

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2. Redfern WS et al. (2003) *Cardiovasc. Res.* **58** : 32-45
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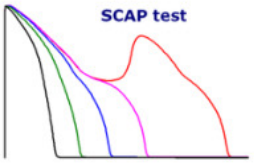

Drug

Lamivudine

Reverse transcriptase inhibitor used to treat HIV and hepatitis B infections

Raw data

IC_{50s} (slope) (1)

I_{CaL} : 54.2 µM (0.89)
I_{to} : ---- µM (---)
I_{Kr} : 2054.0 µM (1.0)
I_{NaL} : ---- µM (---)
I_{Na} : 1571.4 µM (1.0)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ (1)

19.54 µM

TdP risk

Redfern (2) : not reported
Kramer (3) : non-torsadogenic (class 1)
CredibleMeds (4) : not classified with TdP risk (class 4)
CiPA (5) : not reported
WP (6) : 0/2 (TdP+/TdP-)

Results

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

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

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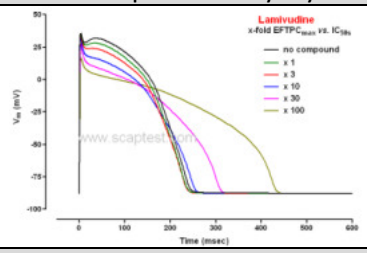
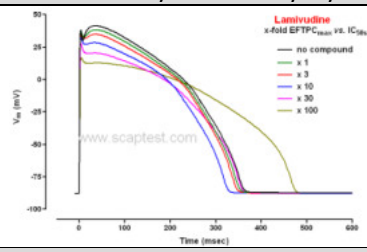
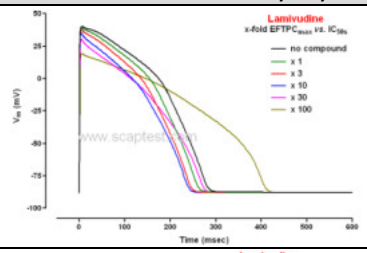
Human epicardial myocytes



Human midmyocardial myocytes



Human endocardial myocytes



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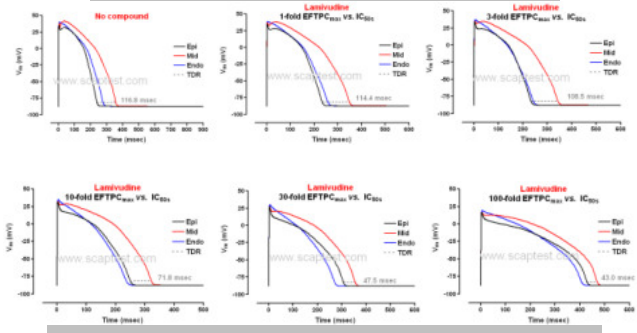

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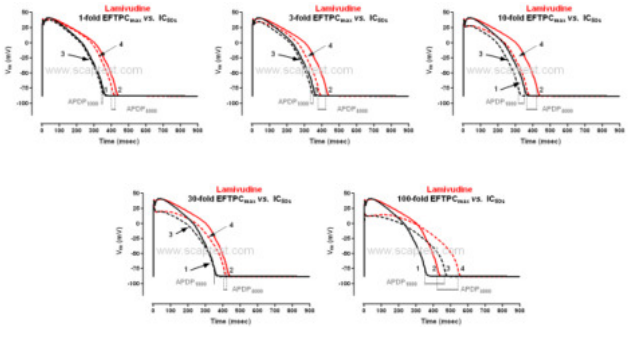
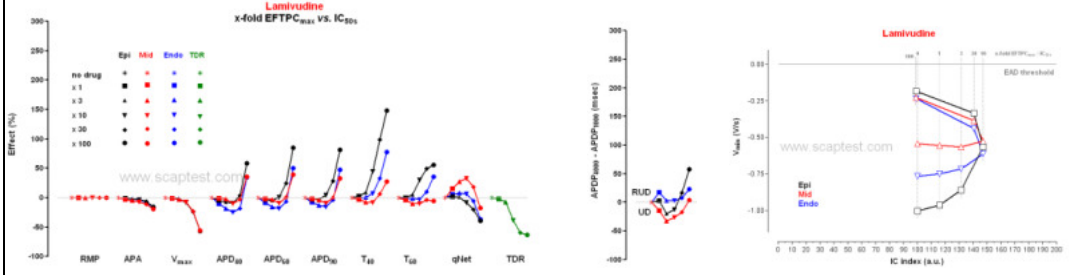


Summary



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2. Redfern WS et al. (2003) *Cardiovasc. Res.* **58** : 32-45
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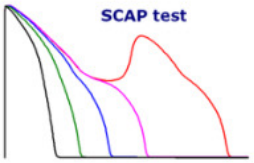

Drug

Lamotrigine

Voltage-gated Na^+ channel ($Na_v1.5$) blocker used to treat some types of epilepsy and bipolar disorder

Raw data

IC_{50s} (slope) (1)

I_{CaL} : 1584.89 µM (1.0)
I_{Kr} : 251.19 µM (1.0)
I_{Na} : 100.0 µM (1.0)
I_{Ks} : 158.49 µM (1.0)
I_{to} : --- µM (---)
I_{NaL} : --- µM (---)
I_{K1} : ---µM (---)

$EFTPC_{max}$ (1)

32.860 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) : 0/1 (TdP+/TdP-)

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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'

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

g = maximal conductance of channel 'j'
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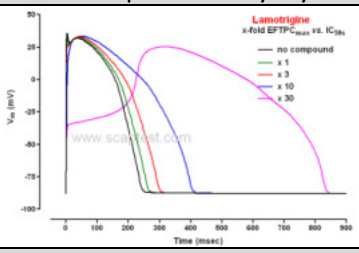
- RUD = $APD_{90}P_{4000}$-$APD_{90}P_{1000}$

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

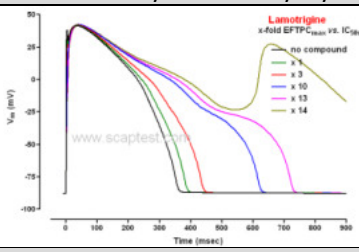
IC index calculation (9):

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

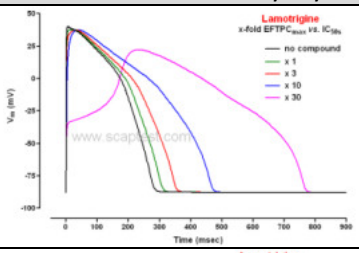
Human epicardial myocytes



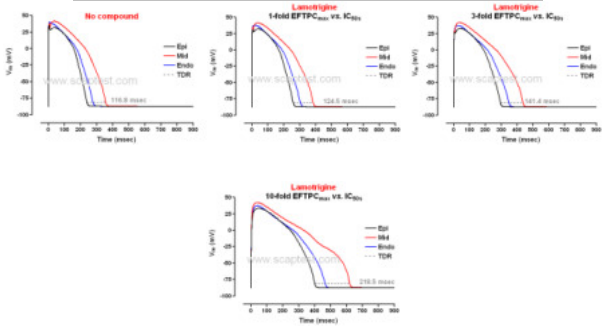
Human midmyocardial myocytes



Human endocardial myocytes

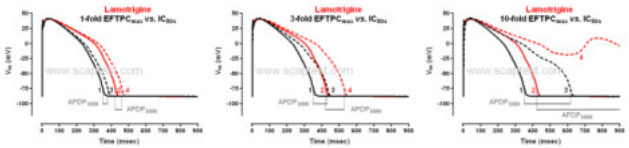


Transmural dispersion of repolarisation

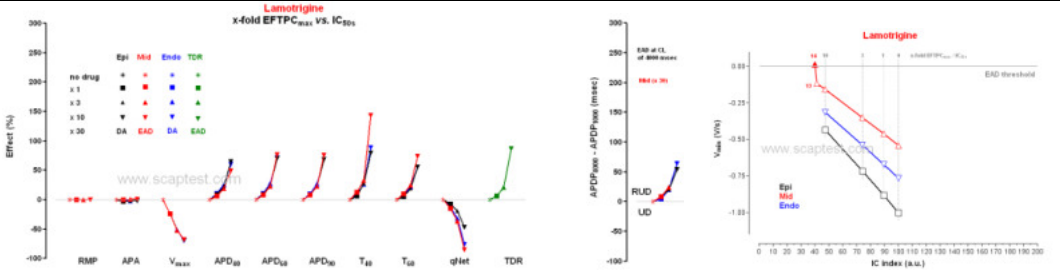


Reverse use dependence on midmyocardial myocytes

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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3. Kramer J et al. (2013) *Sci.rep.* **3** : 2100
4. Woosley RL (2015) www.CredibleMeds.org
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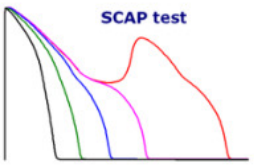
6. Wiśniowska B et al. (2017) *Drug discovery today* **22** : 10-16
7. O'Hara T et al. (2011) *PLoS Comput. Biol.* **7** : e1002061.8
8. Mirams GR et al. (2011) *Cardiovasc. Res.* **91** : 53-61
9. Christophe B & Crumb WJ Jr (2019) *J Pharmacol Toxicol Methods* **96** : 15-26

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_{to}+I_{Na}+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	**Lapatinib** 4-anilinoquinazoline kinase inhibitor used to treat breast cancer

Raw data

IC_{50s} (slope) [1]		$EFTPC_{max}$ [1]	TdP risk
I_{CaL} : 1995.3 µM (1.0)	I_{to} : --- µM (---)	0.03954 µM	Redfern [2] : not reported
I_{Kr} : 1.0 µM (1.0)	I_{NaL} : --- µM (---)		Kramer [3] : not reported
I_{Na} : 3162.3 µM (1.0)	I_{K1} : --- µM (---)		CredibleMeds [4] : possible risk of TdP (class 2)
I_{Ks} : 251.2 µM (1.0)			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}

$$I_j = g\,O\,(V - E_{ion})$$

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'

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

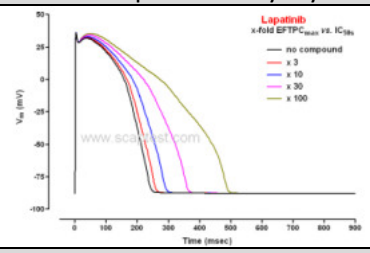
g = maximal conductance of channel 'j'
$g_{control\_j}$ = drug-free maximal conductance of channel 'j'
IC50 = 50% of inhibition of a drug for channel 'j'
D = drug concentration (EFTPC for example)
n = hill slope

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

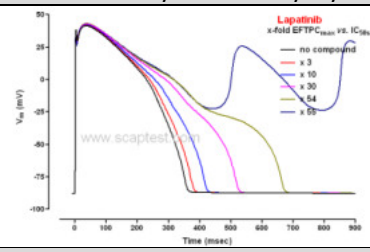
where
$APD_{90}P_x$ = APD_{90} with - APD_{90} without compound at CL x

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}

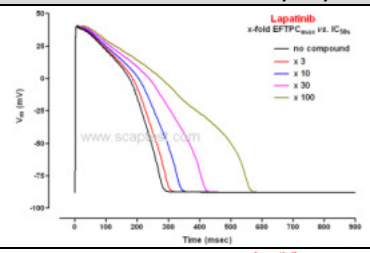
Human epicardial myocytes



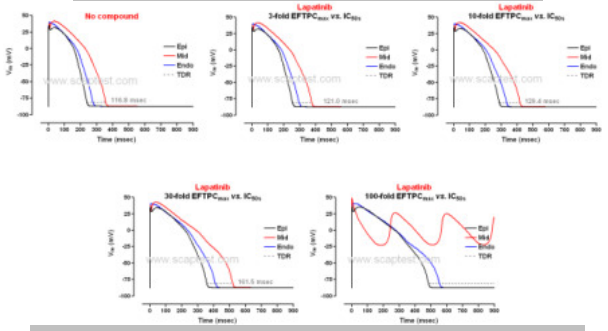
Human midmyocardial myocytes



Human endocardial myocytes

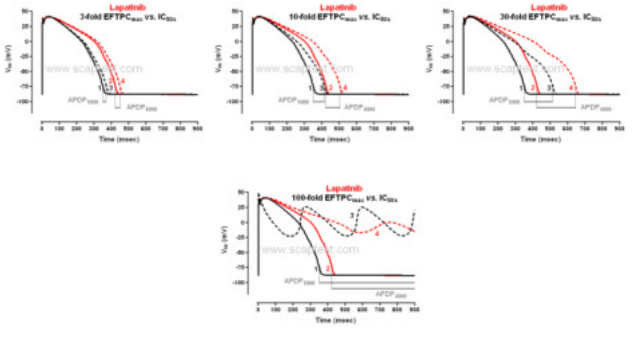


Transmural dispersion of repolarisation

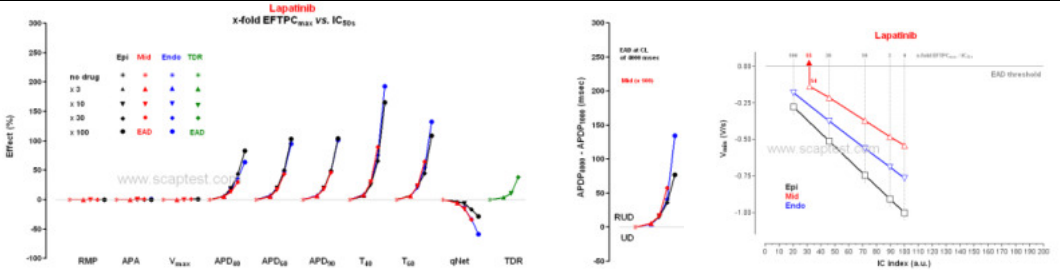


Reverse use dependence on midmyocardial myocytes

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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6. Wiśniowska B et al. (2017) *Drug discovery today* **22** : 10-16
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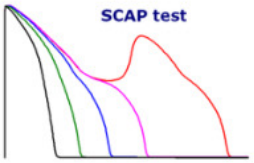
Abbreviations

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_{to}+I_{Na}+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

Levocetirizine

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} : 100.0 µM (1.0)
I_{Na} : ---- µM (---)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ (1)

0.063 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 = 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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- TDR = APD_{90} mid - APD_{90} epi (at CL of 1000 msec)
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IC index = (AFKr/((AFNaL+AFCaL)/2))*100
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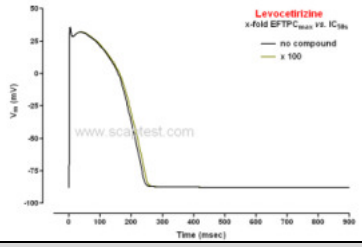
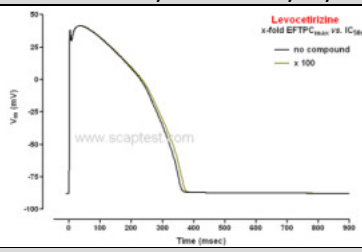
AFKr, AFNaL and AFCaL = active fraction (%) of the I_{Kr}, I_{NaL} and I_{CaL}

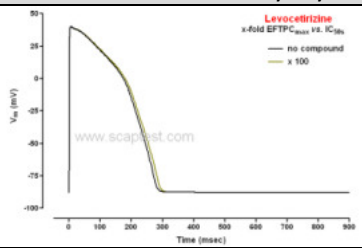
Human epicardial myocytes



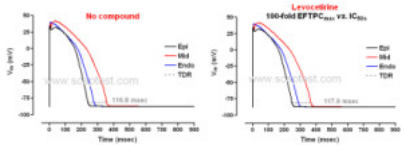
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarisation



Reverse use dependence on midmyocardial myocytes

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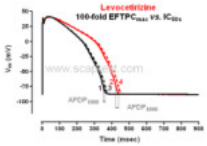
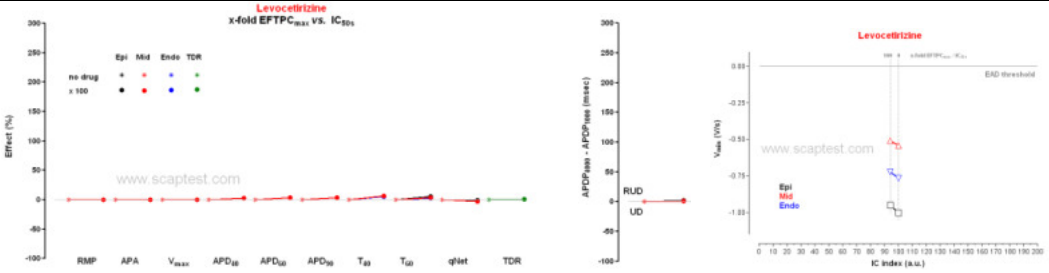


Summary



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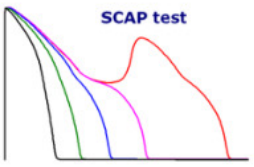

Drug

Levofloxacin

Fluoroquinolone antibiotic used to treat various bacterial infections

Raw data

IC_{50s} (slope) (1)

I_{CaL} : ---- µM (---)
I_{to} : ---- µM (---)
I_{Kr} : 426.58 µM (1.0)
I_{NaL} : ---- µM (---)
I_{Na} : ---- µM (---)
I_{K1} : ---- µM (---)
I_{Ks}: ---- µM (---)

$EFTPC_{max}$ (1)

30.932 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) : 4/0 (TdP+/TdP-)

Results

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

Simulation conditions:

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$g_j = g_{control,j}\left[1 + \left(\frac{D}{IC50}\right)^n\right]^{-1}$ 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)
- RUD = $APD_{90}P_{4000}$-$APD_{90}P_{1000}$

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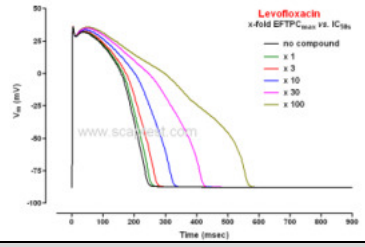
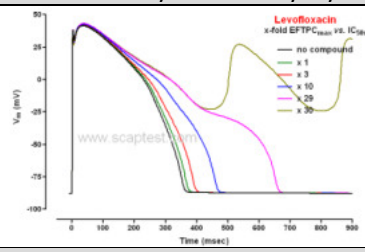
IC index = (AFKr/((AFNaL+AFCaL)/2))*100
where
AFKr, AFNaL and AFCaL = active fraction (%) of the I_{Kr}, I_{NaL} and I_{CaL}

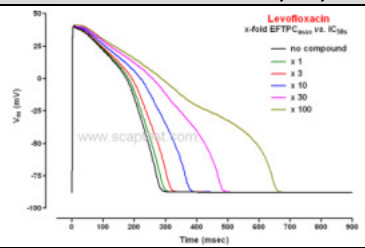
Human epicardial myocytes



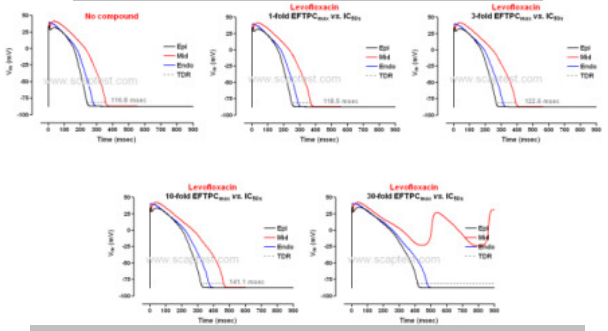
Human midmyocardial myocytes



Human endocardial myocytes

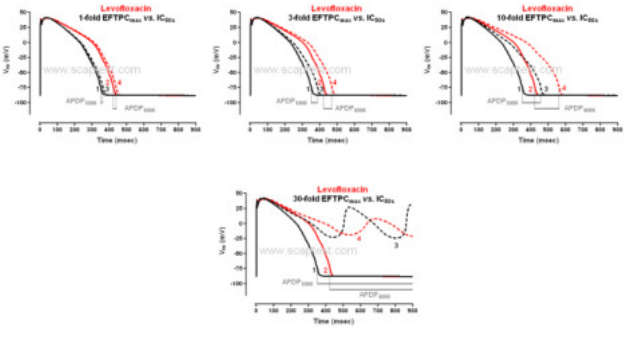


Transmural dispersion of repolarisation

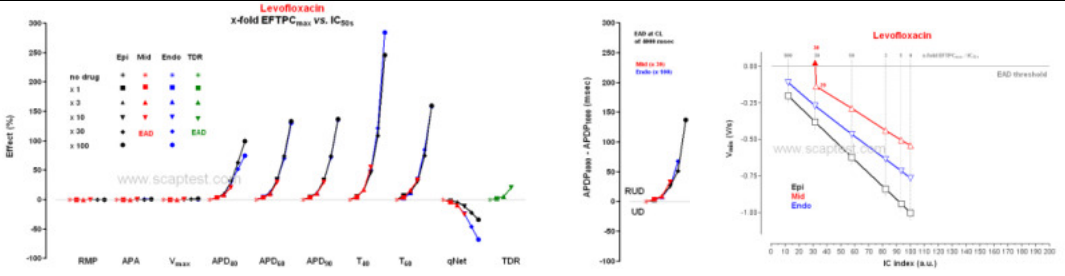


Reverse use dependence on midmyocardial myocytes

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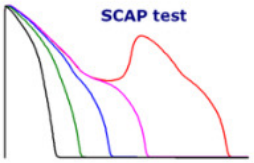
8. Mirams GR et al. (2011) *Cardiovasc. Res.* **91**: 53-61
9. Christophe B & Crumb WJ Jr (2019) *J Pharmacol Toxicol Methods* **96** : 15-26

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_{NaL}+I_{Kr}, **RMP** : resting membrane potential, **RUD** : reverse use dependence, **$T_{40,50}$** : 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

Levosimendan

Troponin C ligand inducing Ca^{++} sensitization used to treat acutely decompensated severe chronic heart failure

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 28.45 µM (1.00)
I_{Kr} : 22.00 µM (0.68)
I_{Na} : 85.714 µM (1.00)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ [1]

0.0028 µM

TdP risk

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

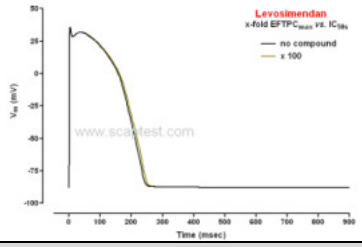
- TDR = APD_{90} mid - APD_{90} epi (at CL of 1000 msec)
- RUD = $APD_{90}P_{4000}$-$APD_{90}P_{1000}$

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

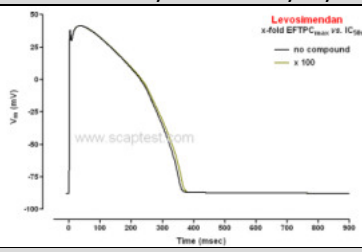
IC index calculation [9]:

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

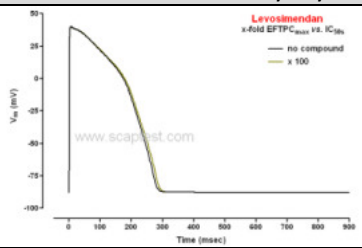
Human epicardial myocytes



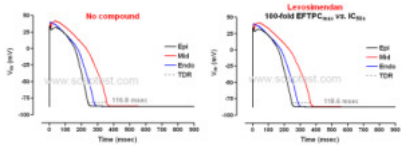
Human midmyocardial myocytes



Human endocardial myocytes

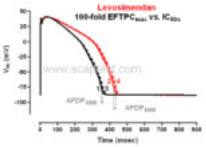


Transmural dispersion of repolarisation

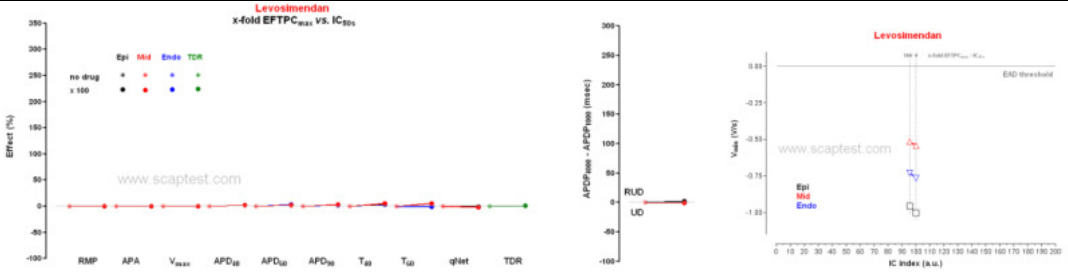


Reverse use dependence on midmyocardial myocytes

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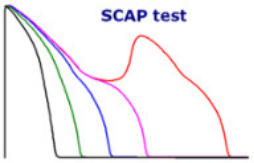

Drug

Lidocaine

Neural Na^+ channel blocker used as local anesthetic

Raw data

IC_{50s} (slope) [1]

I_{CaL} : ---- µM (---)
I_{to} : ---- µM (---)
I_{Kr} : ---- µM (---)
I_{NaL} : 10.79 µM (1.3)
I_{Na} : ---- µM (---)
I_{K1} : ---- µM (---)
I_{Ks}: ---- µM (---)

$EFTPC_{max}$ [1]

2.5604 µM

TdP risk

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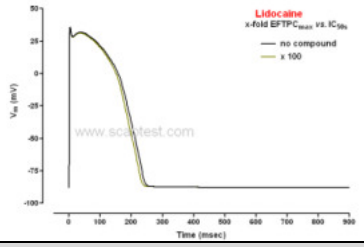
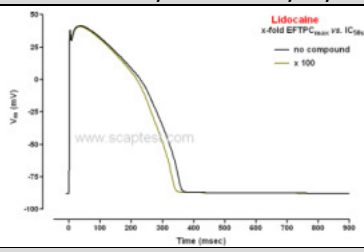
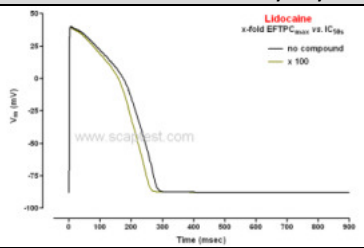
Human epicardial myocytes



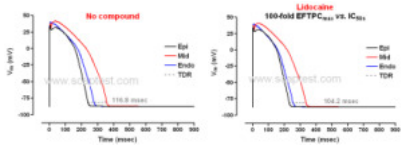
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarisation



Reverse use dependence on midmyocardial myocytes

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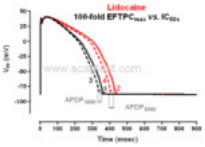

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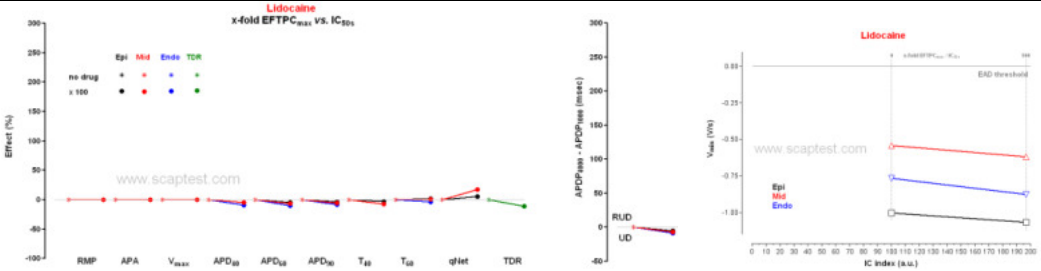

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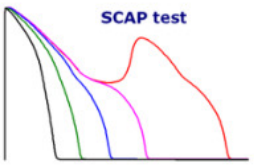

Drug

Linezolid

Oxazolidinone antibiotic used to treat aerobic gram-positive bacterial infections

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 105.4 µM (0.94)
I_{Kr} : 1147.2 µM (1.0)
I_{Na} : 2644.5 µM (1.0)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ [1]

59.11 µM

TdP risk

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

Results

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

Simulation conditions:

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  $[Na^+]_o$ 140 - $[Ca^{++}]_o$ 1.8 - $[K^+]_o$ 5.4
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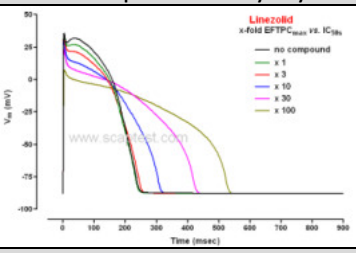
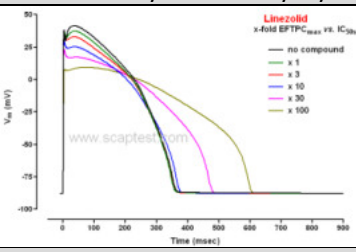
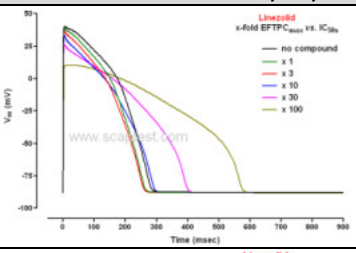
Human epicardial myocytes



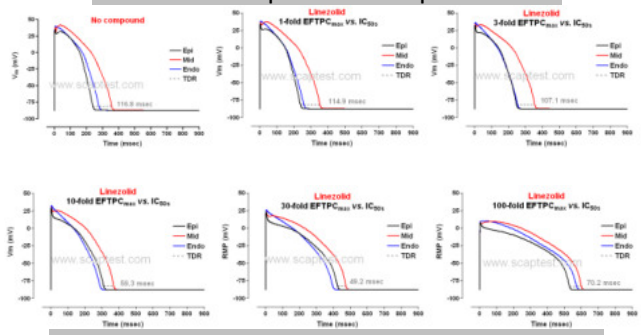
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarisation



Reverse use dependence on midmyocardial myocytes

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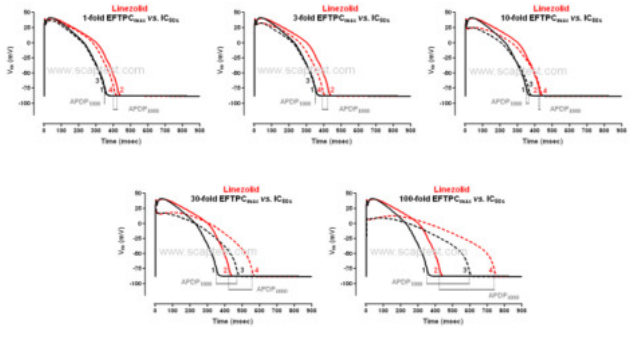
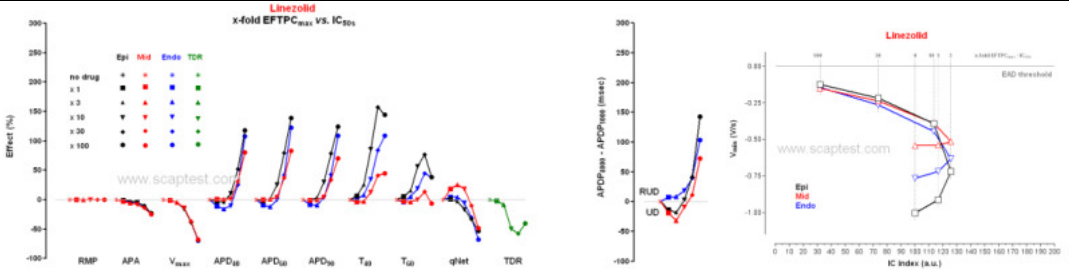


Summary



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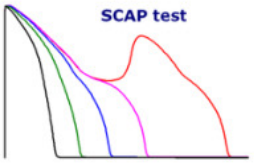

Drug

Lopinavir

HIV-1 protease inhibitor used to treat HIV infection

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 15.601 µM (1.0)
I_{to} : ---- µM (---)
I_{Kr} : 5.17µM (1.2)
I_{NaL} : ---- µM (---)
I_{Na} : ---- µM (---)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ [1]

0.7037 µM

TdP risk

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

Results

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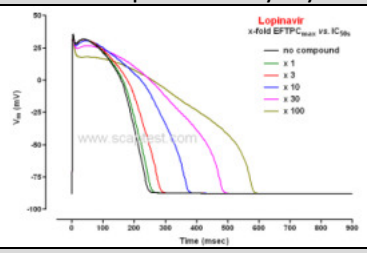
- RUD = $APD_{90}P_{4000}$- $APD_{90}P_{1000}$

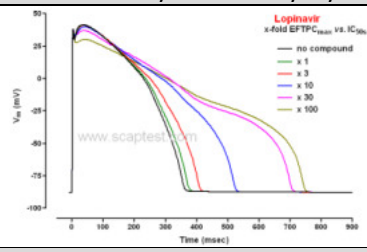
where
$APD_{90}P_x$ = APD_{90} with - APD_{90} without compound at CL x

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

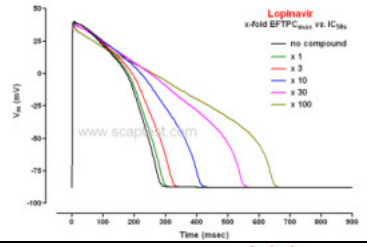
Human epicardial myocytes



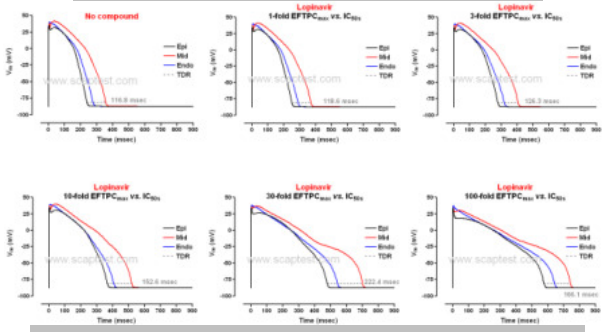
Human midmyocardial myocytes



Human endocardial myocytes

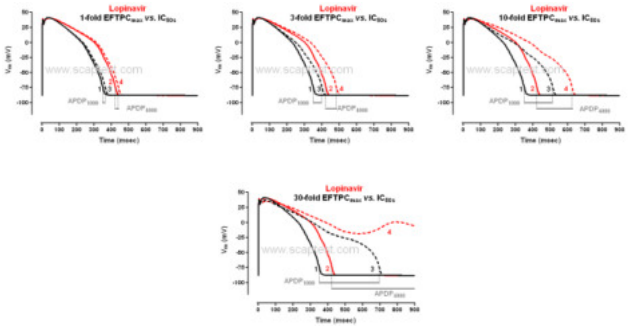


Transmural dispersion of repolarisation

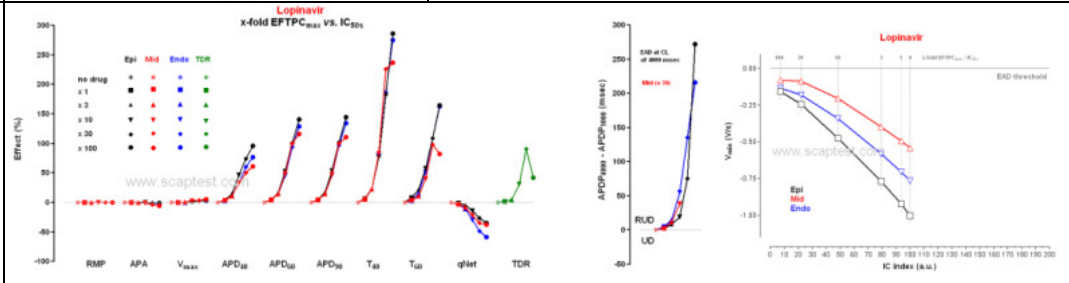


Reverse use dependence on midmyocardial myocytes

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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3. Kramer J et al. (2013) *Sci.rep.* **3** : 2100
4. Woosley RL (2015) www.CredibleMeds.org
5. CIPA (2016) www.lhsiextra.org/hesi/science/cardiac/cipa/Project
6. Wiśniowska B et al. (2017) *Drug discovery today* **22** : 10-16
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9. Christophe B & Crumb WJ Jr (2019) *J Pharmacol Toxicol Methods* **96** : 15-26

Abbreviations

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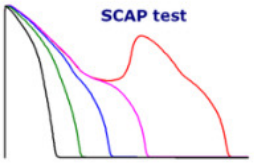

Drug

Loratadine

Histamine H_1 receptor antagonist used to treat allergic rhinitis

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 11.4 µM (1.38)
I_{Kr} : 6.1 µM (1.44)
I_{Na} : 28.9 µM (1.64)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ [1]

0.0004 µM

TdP risk

Redfern [2] : no published report of TdP (class 5)
Kramer [3] : non-torsadogenic (class 1)
CredibleMeds [4] : not classified with TdP risk (class 4)
CiPA [5] : low or no risk of TdP (class 3)
WP [6] : 0/7 (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}

$I_j = g\,O(V - E_{ion})$ (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)

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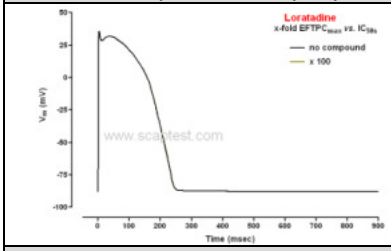
- RUD = $APD_{90}P_{4000}$-$APD_{90}P_{1000}$

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

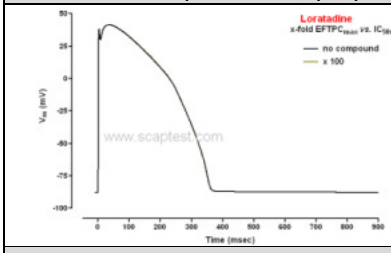
IC index calculation [9]:

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

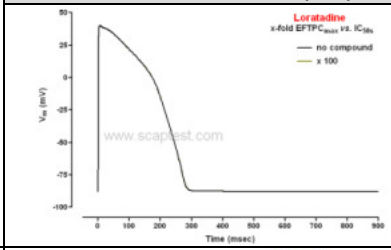
Human epicardial myocytes



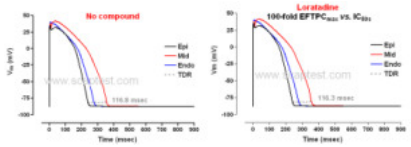
Human midmyocardial myocytes



Human endocardial myocytes

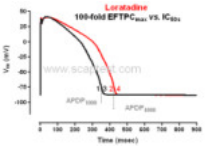


Transmural dispersion of repolarisation

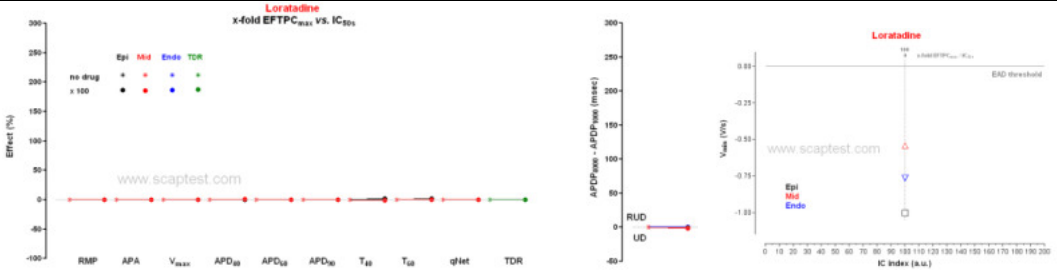


Reverse use dependence on midmyocardial myocytes

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
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Abbreviations

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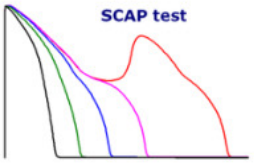

Drug

Maraviroc

Human chemokine CCR5 receptor antagonist used to treat HIV infection

Raw data

IC_{50s} (slope) [1]

I_{CaL} : ---- µM (---)
I_{to} : ---- µM (---)
I_{Kr} : 39.81 µM (1.0)
I_{NaL} : ---- µM (---)
I_{Na} : 1000.0 µM (1.0)
I_{K1} : ---- µM (---)
I_{Ks} : 63.096 µM (1.0)

$EFTPC_{max}$ [1]

0.10981 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
- 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'

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

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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 = APD_{90} mid - APD_{90} epi (at CL of 1000 msec)
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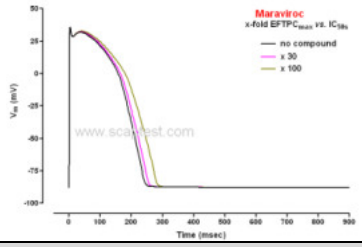
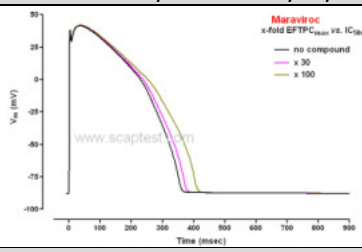
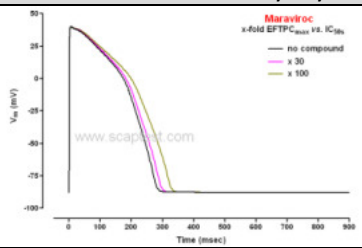
Human epicardial myocytes



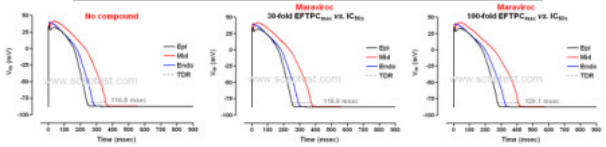
Human midmyocardial myocytes



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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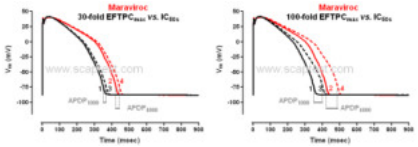
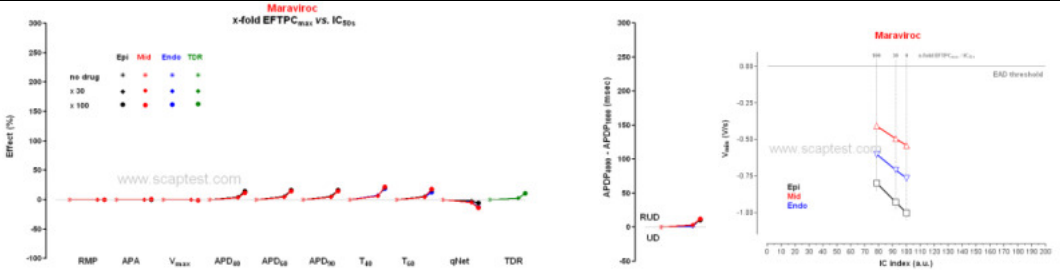


Summary



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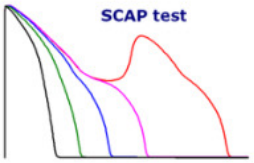

Drug

Mefloquine

Mechanism of action not fully understood, used to treat malaria

Raw data

IC_{50s} (slope) [1]

I_{CaL} : ---- µM (---)
I_{to} : ---- µM (---)
I_{Kr} : 14.1 µM (1.0)
I_{NaL} : ---- µM (---)
I_{Na} : ---- µM (---)
I_{K1} : ---- µM (---)
I_{Ks} : 1.43 µM (1.0)

$EFTPC_{max}$ [1]

0.0952 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] : 2/2 (TdP+/TdP-)

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where
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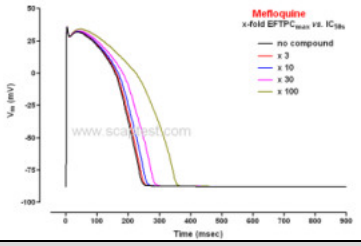
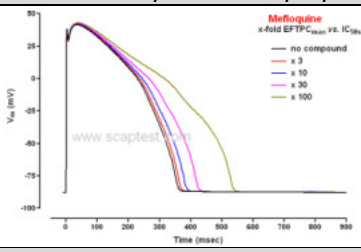
where
AFKr, AFNaL and AFCaL = active fraction (%) of the I_{Ks}, I_{NaL} and I_{CaL}.

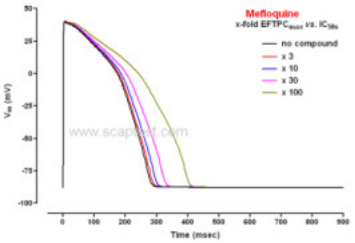
Human epicardial myocytes



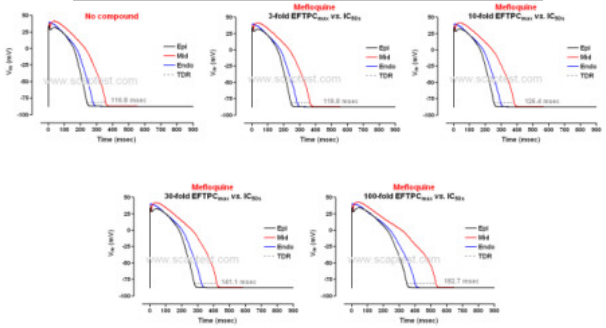
Human midmyocardial myocytes



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
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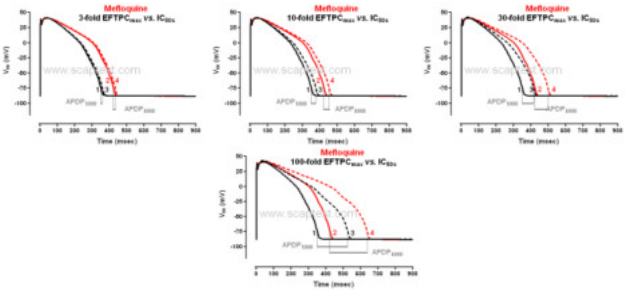
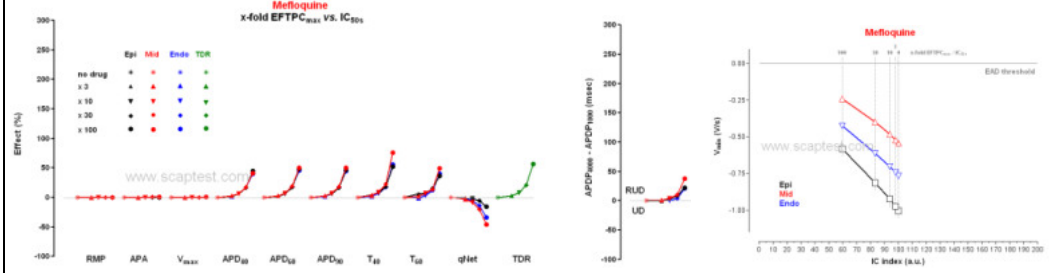


Summary



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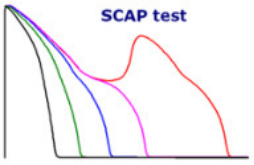
6. Wiśniowska B et al. (2017) *Drug discovery today* **22**: 10-16
7. O'Hara T et al. (2011) *PLoS Comput. Biol.* **7**: e1002061_8
8. Mirams GR et al. (2011) *Cardiovasc. Res.* **91**: 53-61
9. Christophe B & Crumb WJ Jr (2019) *J Pharmacol Toxicol Methods* **96**: 15-26

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_{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

Methadone

Opioid κ and σ receptor antagonist used to treat severe pain

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 37.4 µM (1.67)
I_{Kr} : 3.5 µM (1.0)
I_{Na} : 31.8 µM (1.37)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ [1]

0.507 µM

TdP risk

Redfern [2] : not reported
Kramer [3] : torsadogenic (class 2)
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}

$$I_j = g\,O(V - E_{ion})$$

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:

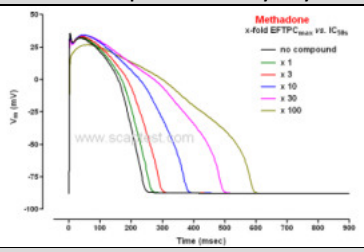
- TDR = APD_{90} mid - APD_{90} epi (at CL of 1000 msec)
- RUD = $APD_{90}P_{4000}$-$APD_{90}P_{1000}$

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

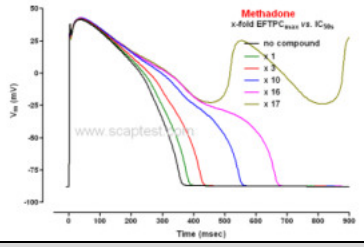
IC index calculation [9]:

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

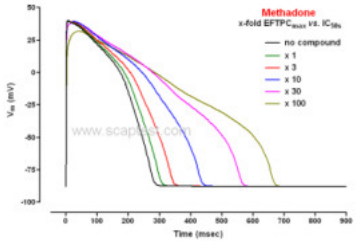
Human epicardial myocytes



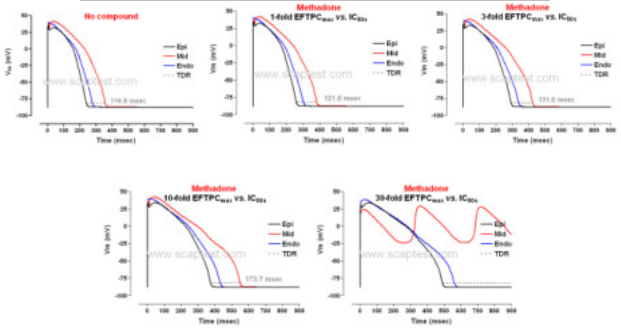
Human midmyocardial myocytes



Human endocardial myocytes

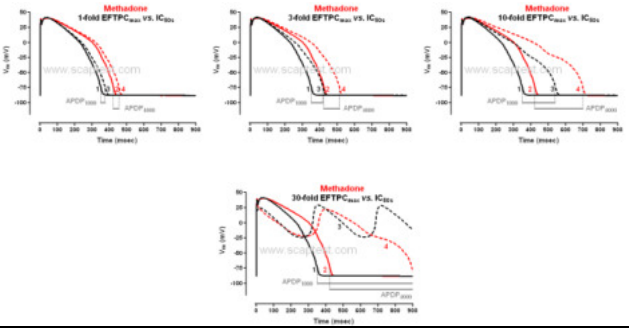


Transmural dispersion of repolarisation

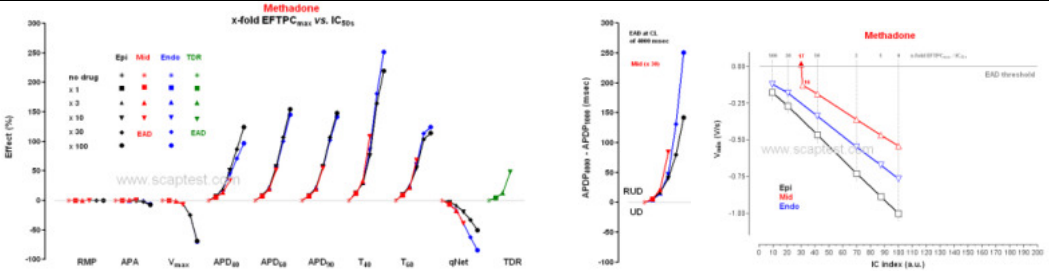


Reverse use dependence on midmyocardial myocytes

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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3. Kramer J et al. (2013) *Sci.rep.* **3** : 2100
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6. Wiśniowska B et al. (2017) *Drug discovery today* **22** : 10-16
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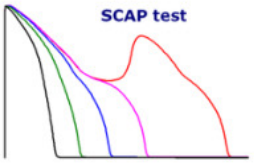
Abbreviations

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_{Na}+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	**Metoprolol** β_1-adrenoceptor antagonist used to treat hypertension and angina, and to reduce mortality due to myocardial infarction

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 3280 µM (1.0) — I_{to} : ---- µM (---)
I_{Kr} : ---- µM (---) — I_{NaL} : 630.0 µM (1.0)
I_{Na} : 30.3 µM (1.0) — I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ [1]

1.80 µM

TdP risk

Redfern [2] : not reported
Kramer [3] : not reported
CredibleMeds [4] : not classified with TdP risk (class 4)
CiPA [5] : low or no risk of TdP (class 3)
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}

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

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

TDR and RUD estimation:
- TDR = APD_{90} mid - APD_{90} epi (at CL of 1000 msec)
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IC index calculation [9]:
IC index = (AFKr/((AFNaL+AFCaL)/2))*100
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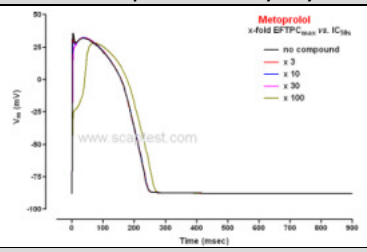
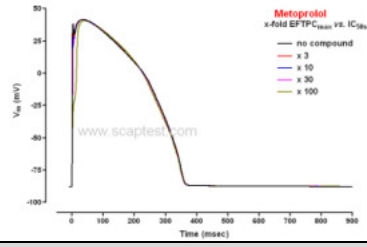
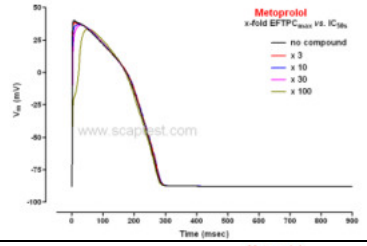
Human epicardial myocytes



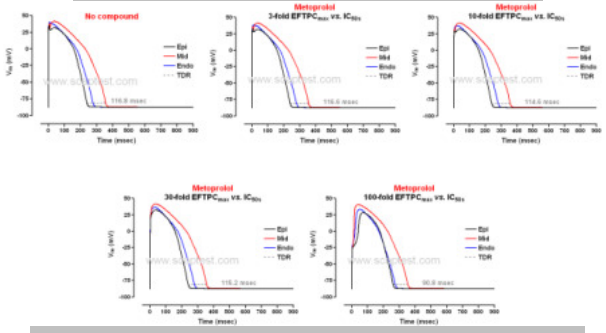
Human midmyocardial myocytes



Human endocardial myocytes

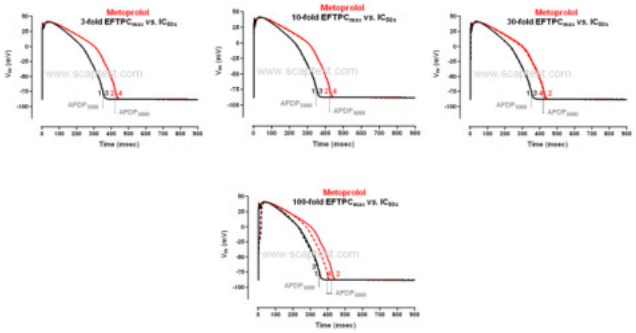


Transmural dispersion of repolarisation

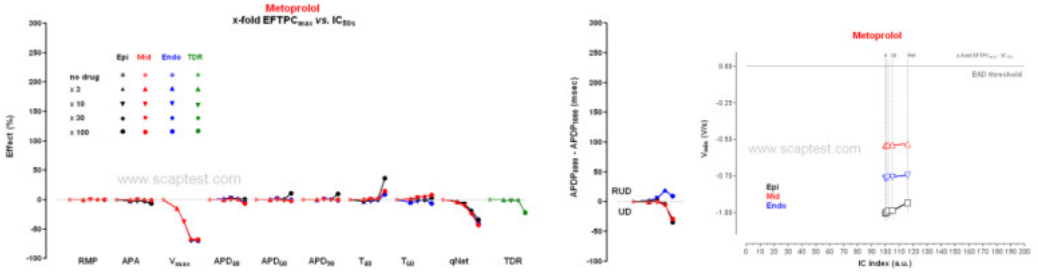


Reverse use dependence on midmyocardial myocytes

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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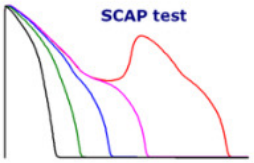


Drug

Metronidazole

Mechanism of action not fully understood, used to treat trichomoniasis, amebiasis and bacterial infections

Raw data

IC_{50s} (slope) (1)

I_{CaL} : 177.9 µM (0.66)
I_{to} : ---- µM (---)
I_{Kr} : 1340.2 µM (1.0)
I_{NaL} : ---- µM (---)
I_{Na} : 2073.2 µM (1.0)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ (1)

187.0 µM

TdP risk

Redfern (2) : not reported
Kramer (3) : non-torsadogenic (class 1)
CredibleMeds (4) : conditional risk of TdP (class 3)
CiPA (5) : not reported
WP (6) : 1/3 (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)

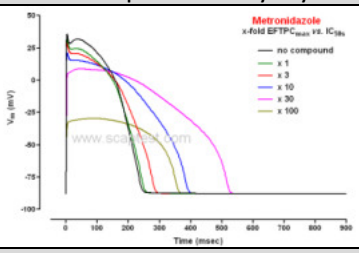
$g_j = g_{control,j}\left[1 + \left(\frac{D}{IC50_j}\right)^n\right]^{-1}$ (g = maximal conductance of channel j; $g_{control,j}$ = drug free maximal conductance of channel j; IC50 = 50% of inhibition of a drug for channel j; D= drug concentration (EFTPC for example); n= hill slope)

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

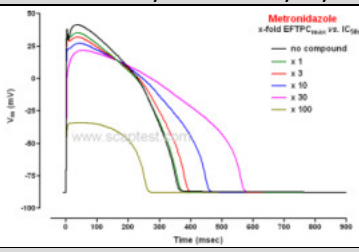
where
$APD_{90}P_x$ = APD_{90} with - APD_{90} without compound at CL x

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}.

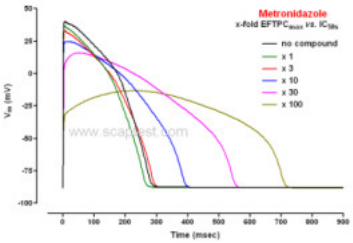
Human epicardial myocytes



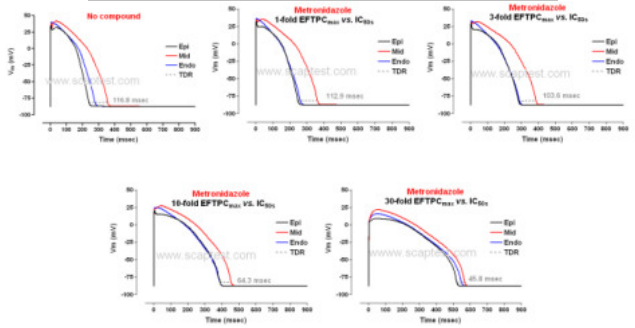
Human midmyocardial myocytes



Human endocardial myocytes

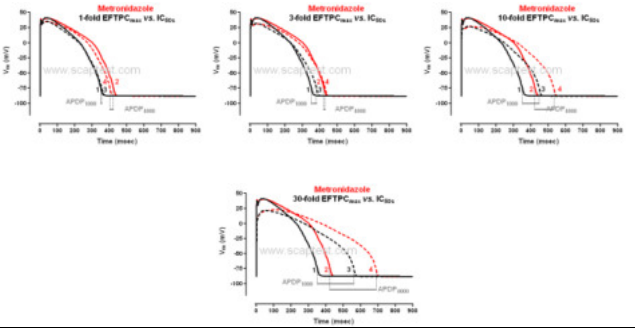


Transmural dispersion of repolarisation

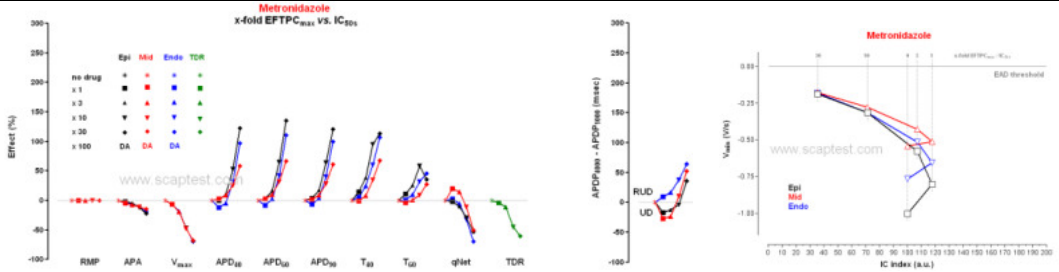


Reverse use dependence on midmyocardial myocytes

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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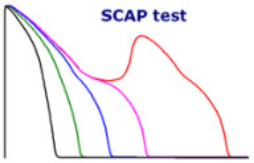


Drug

Mexiletine

Voltage-gated Na^+ channel blocker used as class IB antiarrhythmic to treat ventricular arrhythmia

Raw data

IC_{50s} (slope) (1)

I_{CaL} : ---- µM (---)
I_{to} : ---- µM (---)
I_{Kr} : ---- µM (---)
I_{NaL} : 8.957 µM (1.4)
I_{Na} : ---- µM (---)
I_{K1} : ---- µM (---)
I_{Ks}: ---- µM (---)

$EFTPC_{max}$ (1)

2.5032 µM

TdP risk

Redfern (2) : isolated reports of TdP (class 4)
Kramer (3) : not reported
CredibleMeds (4) : not classified with TdP risk (class 4)
CiPA (5) : low or no risk of TdP (class 3)
WP (6) : 1/5 (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}

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

TDR and RUD estimation:

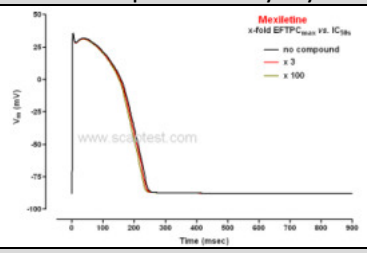
- TDR = APD_{90} mid - APD_{90} epi (at CL of 1000 msec)
- RUD = $APD_{90}P_{4000}$-$APD_{90}P_{1000}$

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

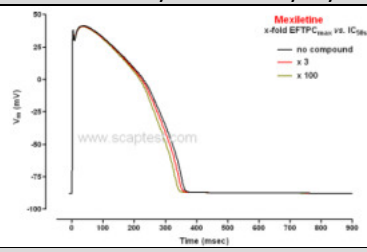
IC index calculation (9):

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

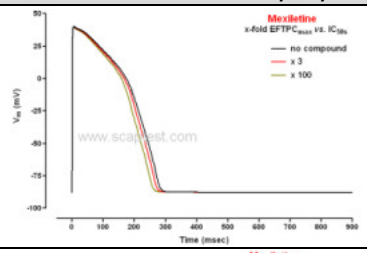
Human epicardial myocytes



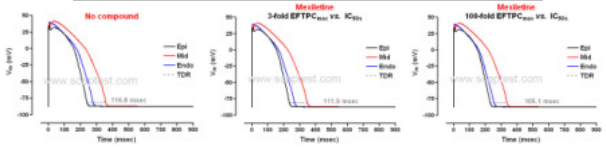
Human midmyocardial myocytes



Human endocardial myocytes

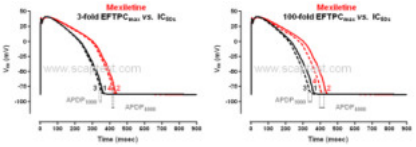


Transmural dispersion of repolarisation



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



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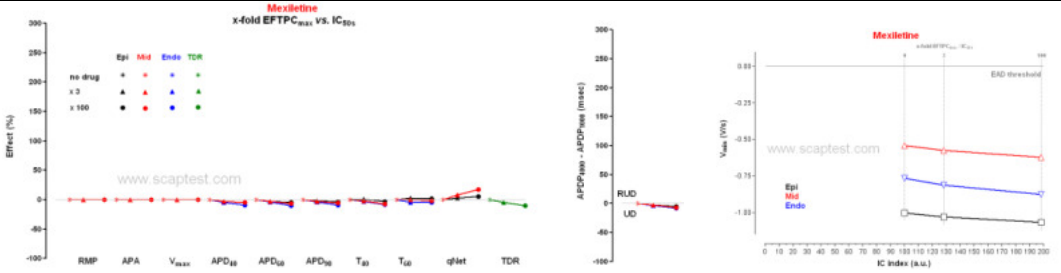

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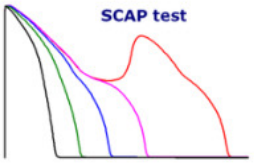

Drug

Mibefradil

Voltage-gated T- and L-type Ca^{++} channel blocker
no longer marketed in USA and UK (Onakpoya et al (2016) *BMC Med.* **14**: 10)

Raw data

IC_{50s} (slope) (1)

I_{CaL} : 0.51 µM (1.44)
I_{Kr} : 1.7 µM (1.38)
I_{Na} : 5.6 µM (1.53)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ (1)

0.012 µM

TdP risk

Redfern (2) : isolated TdP reports (class 4)
Kramer (3) : non-torsadogenic (class 1)
CredibleMeds (4) : not reported
CiPA (5) : not reported
WP (6) : 3/4 (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_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'

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

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

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

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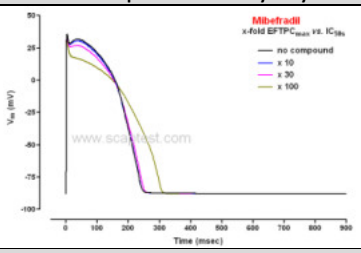
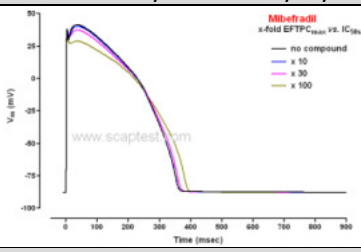
IC index = (AFKr/((AFNaL+AFCaL)/2))*100
where
AFKr, AFNaL and AFCaL = active fraction (%) of the I_{Kr}, I_{NaL} and I_{CaL}

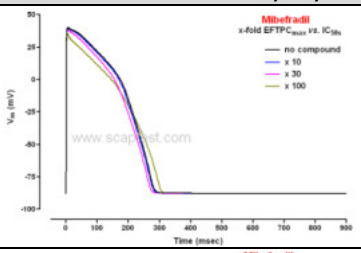
Human epicardial myocytes



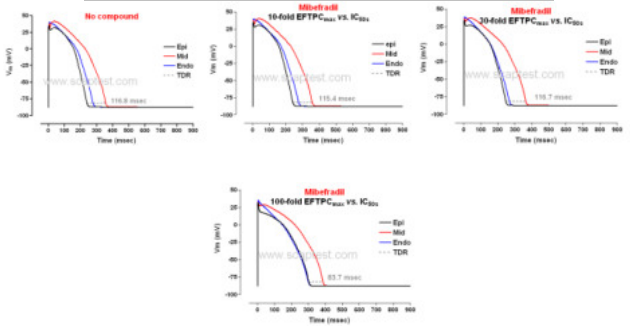
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarisation



Reverse use dependence on midmyocardial myocytes

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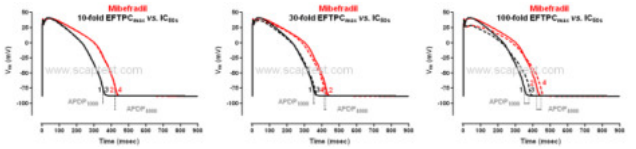
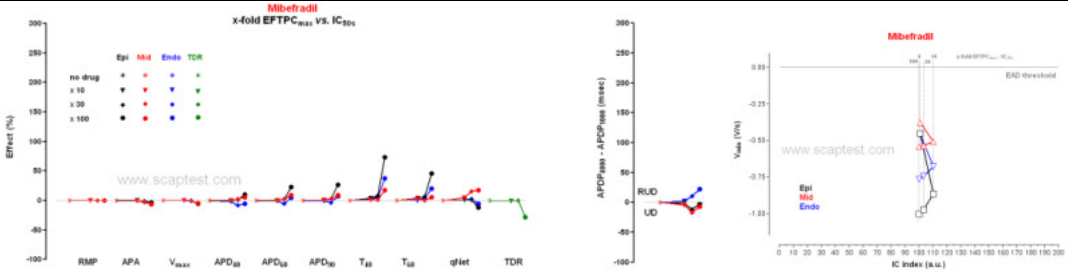


Summary



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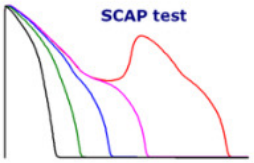

Drug

Milrinone

Phosphodiesterase PDE-III inhibitor used to treat acute decompensated heart failure

Raw data

IC_{50s} (slope) (1)

I_{CaL} : ---- µM (---)
I_{Kr} : 1500.0 µM (0.85)
I_{Na} : ---- µM (---)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ (1)

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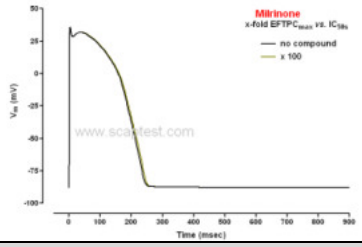
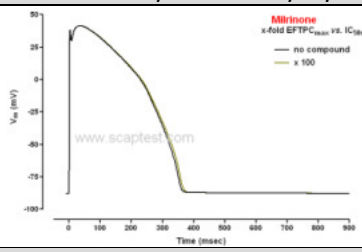
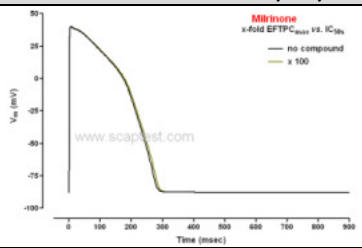
Human epicardial myocytes



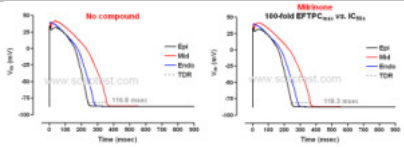
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarisation



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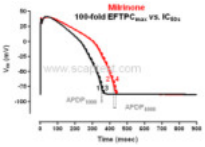

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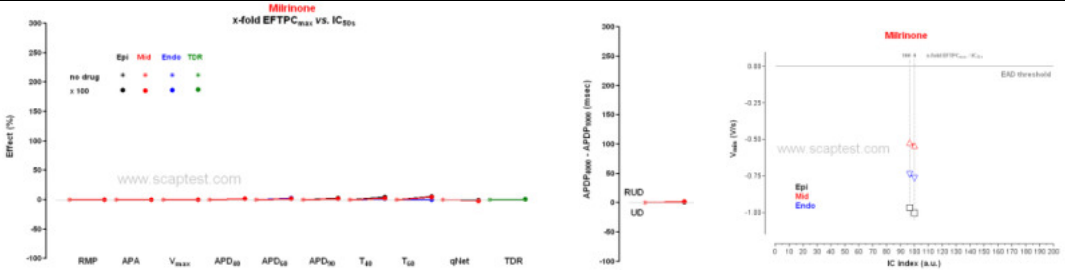

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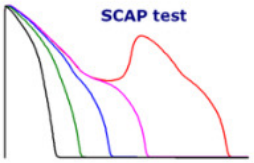

Drug

Mitoxantrone

DNA reactive agent used to treat multiple sclerosis

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 22.5 µM (0.64)
I_{to} : ---- µM (---)
I_{Kr} : 539.4 µM (1.0)
I_{NaL} : ---- µM (---)
I_{Na} : 93.5 µM (1.05)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ [1]

0.225 µM

TdP risk

Redfern [2] : not reported
Kramer [3] : non-torsadogenic (class 1)
CredibleMeds [4] : not classified with TdP risk (class 4)
CiPA [5] : not reported
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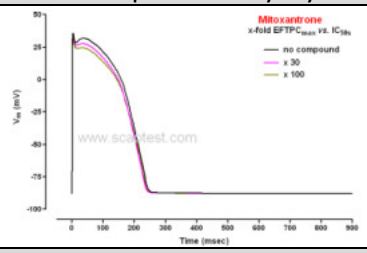
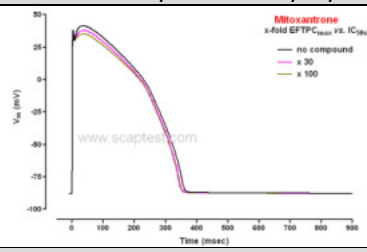
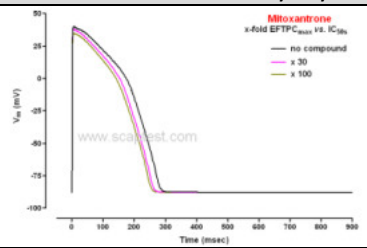


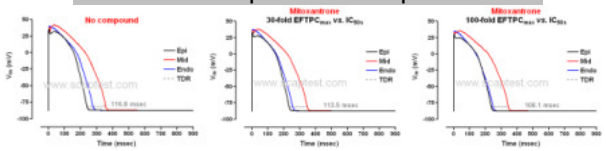
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarisation



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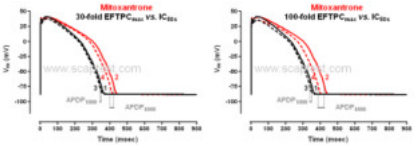
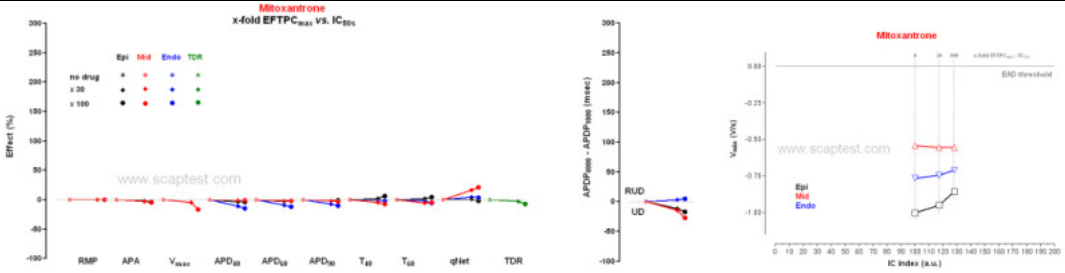


Summary



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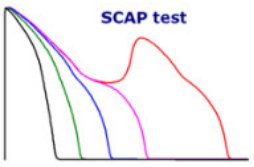
9. Christophe B & Crumb WJ Jr (2019) *J Pharmacol Toxicol Methods* **96** : 15-26

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_{to}+I_{Na}+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

Moxifloxacin

Fluoroquinolone antibiotic used to treat various bacterial infections

Raw data

IC_{50s} (slope) (1)

I_{CaL} : 173.0 µM (1.0)
I_{to} : ---- µM (---)
I_{Kr} : 86.2 µM (0.94)
I_{NaL} : ---- µM (---)
I_{Na} : 1112.0 µM (1.0)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ (1)

10.96 µM

TdP risk

Redfern (2) : not reported
Kramer (3) : torsadogenic (class 2)
CredibleMeds (4) : known risk of TdP (class 1)
CiPA (5) : not reported
WP (6) : 8/4 (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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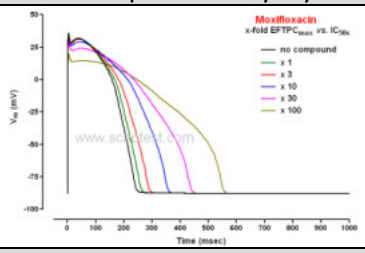
- TDR = APD_{90} mid - APD_{90} epi (at CL of 1000 msec)
- RUD = $APD_{90}P_{x000}$-$APD_{90}P_{1000}$

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

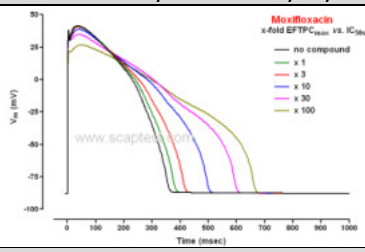
IC index calculation (9):

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

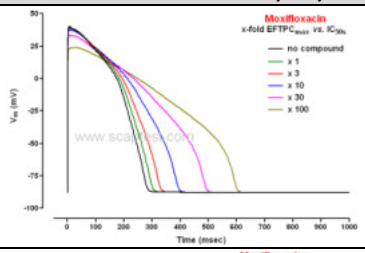
Human epicardial myocytes



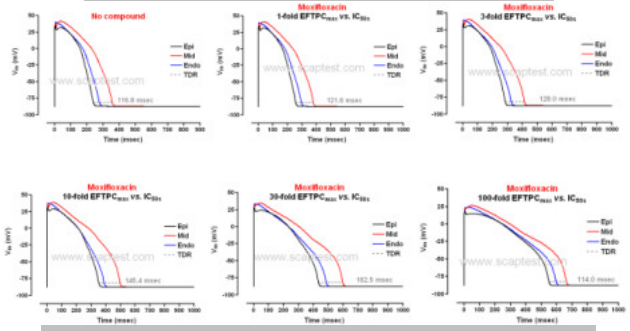
Human midmyocardial myocytes



Human endocardial myocytes

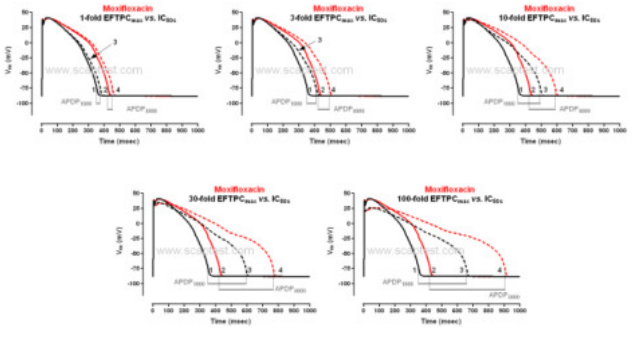


Transmural dispersion of repolarisation

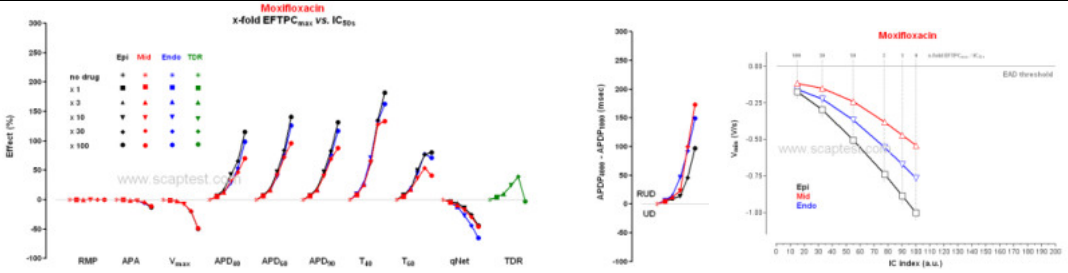


Reverse use dependence on midmyocardial myocytes

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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Abbreviations

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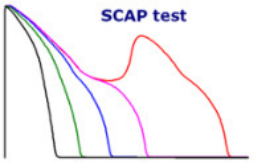

Drug

Nebivolol

β_1-adrenoceptor antagonist used to treat hypertension and heart failure

Raw data

IC_{50s} (slope) [1]

I_{CaL} : ---- µM (---)
I_{Kr} : 0.316 µM (1.0)
I_{Na} : 6.310 µM (1.0)
I_{Ks} : 15.849 µM (1.0)
I_{to} : 50.119 µM (1.0)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ [1]

0.00094 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}

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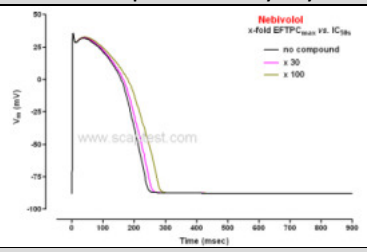
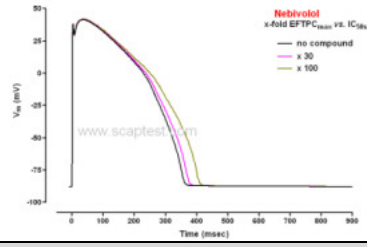
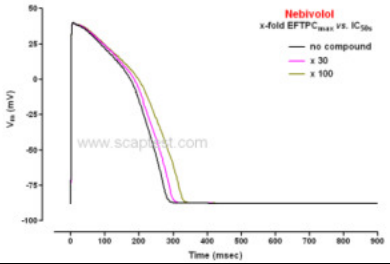
Human epicardial myocytes



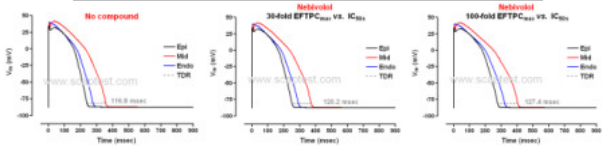
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarisation



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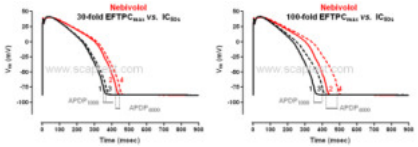

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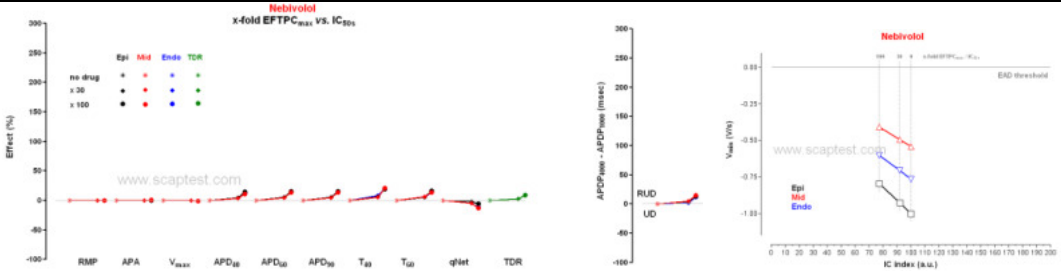

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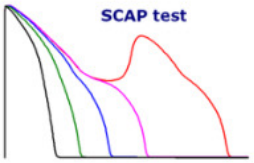

Drug

Nelfinavir

Viral protease inhibitor used to treat HIV infection

Raw data

IC_{50s} (slope) [1]

I_{CaL} : --- µM (---)
I_{Kr} : 12.589 µM (1.0)
I_{Na} : 79.433 µM (1.0)
I_{Ks} : 79.433 µM (1.0)
I_{to} : 5011.87 µM (1.0)
I_{NaL} : --- µM (---)
I_{K1} : --- µM (---)

$EFTPC_{max}$ [1]

0.0710 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] : 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
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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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where
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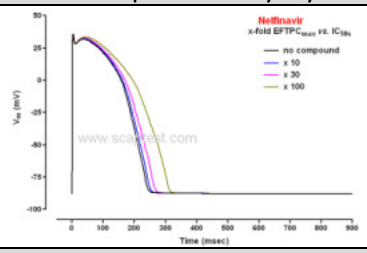
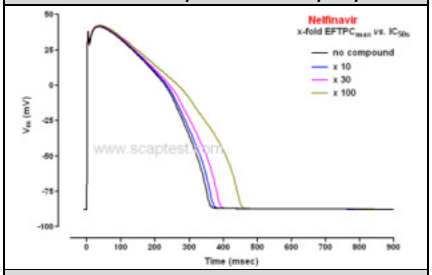
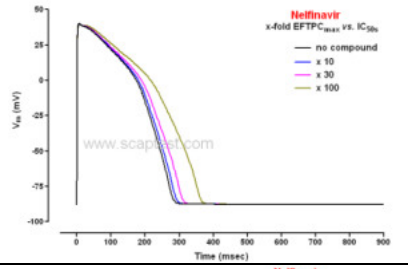
Human epicardial myocytes



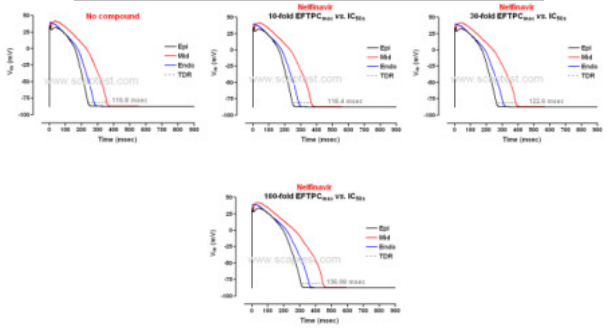
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarisation



Reverse use dependence on midmyocardial myocytes

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2 - CL 4000 msec without compound
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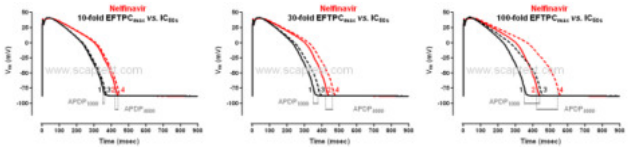
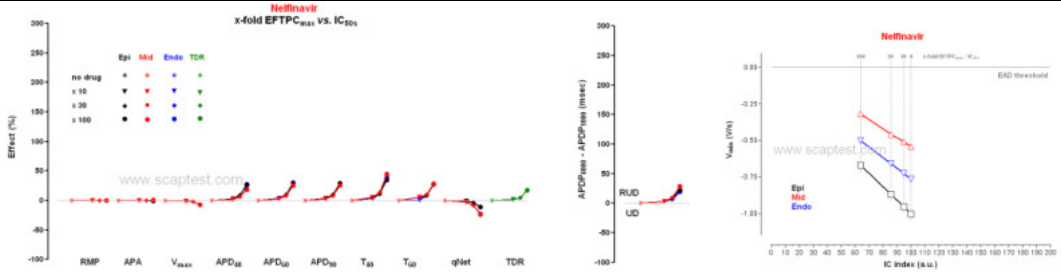


Summary



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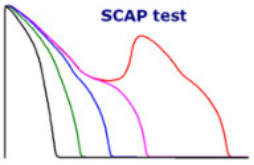

Drug

Nicardipine

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

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 0.0097 µM (1.0)
I_{Kr} : 0.3 µM (1.11)
I_{Na} : 1.02 µM (1.0)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ [1]

0.014 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] : 1/2 (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
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$$I_j = g_j O(V - E_{ion})$$

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TDR and RUD estimation:

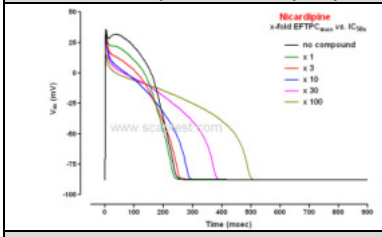
- TDR = APD_{90} mid - APD_{90} epi (at CL of 1000 msec)
- RUD = $APD_{90}P_{4000}$-$APD_{90}P_{1000}$

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

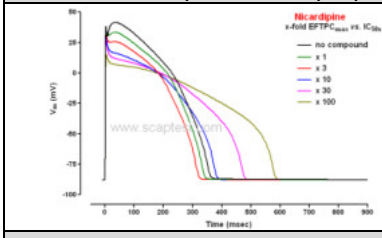
IC index calculation [9]:

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

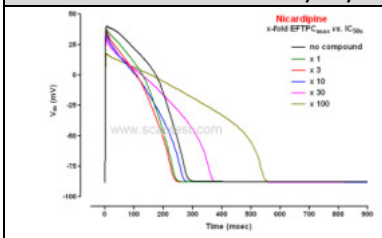
Human epicardial myocytes



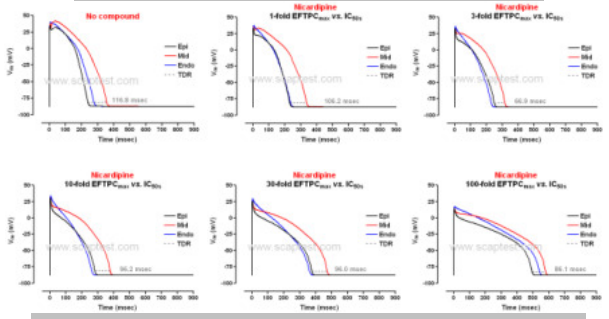
Human midmyocardial myocytes



Human endocardial myocytes

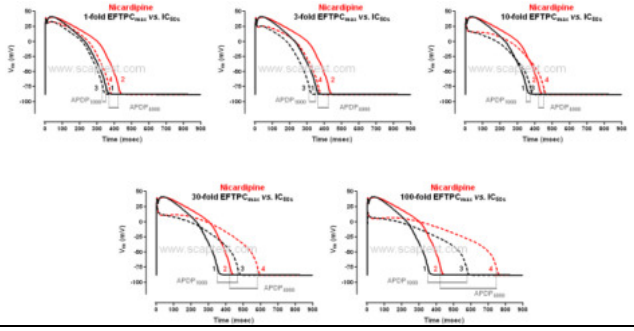


Transmural dispersion of repolarisation

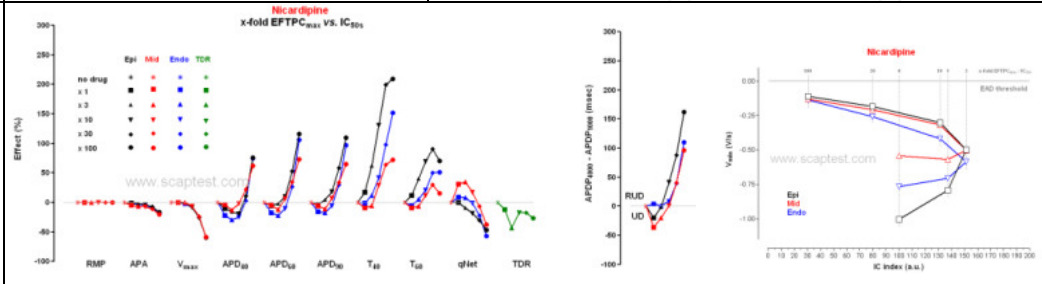


Reverse use dependence on midmyocardial myocytes

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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4. Woosley RL (2015) www.CredibleMeds.org
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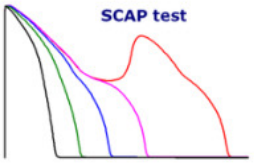
7. O'Hara T et al. (2011) *PLoS Comput. Biol.* **7**: e1002061.8
8. Mirams GR et al. (2011) *Cardiovasc. Res.* **91**: 53-61
9. Christophe B & Crumb WJ Jr (2019) *J Pharmacol Toxicol Methods* **96** : 15-26

Abbreviations

AP : action potential, **APA** : AP amplitude, $\mathbf{APD_{40,60\ or\ 90}}$: 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

Nifedipine

Voltage-gated L-type Ca^{++} channel ($Ca_v1.2$) blocker used to treat hypertension and angina
no longer marketed in Australia (Onakpoya et al (2016) *BMC Med.* **14**: 10))

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 0.012 µM (1.02)
I_{Kr} : 44.0 µM (0.80)
I_{Na} : 88.5 µM (0.71)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ [1]

0.008 µM

TdP risk

Redfern [2] : isolated TdP reports (class 4)
Kramer [3] : non-torsadogenic (class 1)
CredibleMeds [4] : not classified with TdP risk (class 4)
CiPA [5] : low or no risk of TdP (class 3)
WP [6] : 0/7 (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:

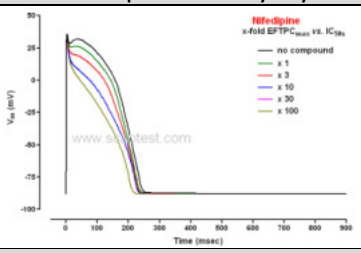
- TDR = APD_{90} mid - APD_{90} epi (at CL of 1000 msec)
- RUD = $APD_{90}P_{4000}$-$APD_{90}P_{1000}$

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

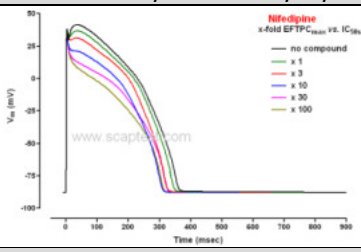
IC index calculation [9]:

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

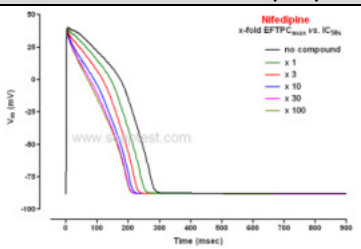
Human epicardial myocytes



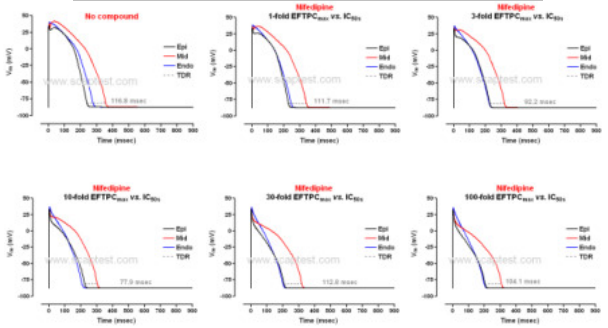
Human midmyocardial myocytes



Human endocardial myocytes

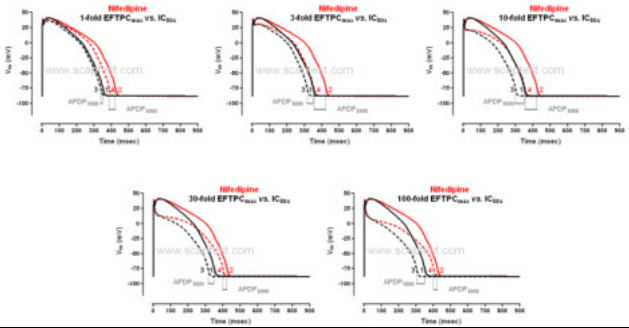


Transmural dispersion of repolarisation

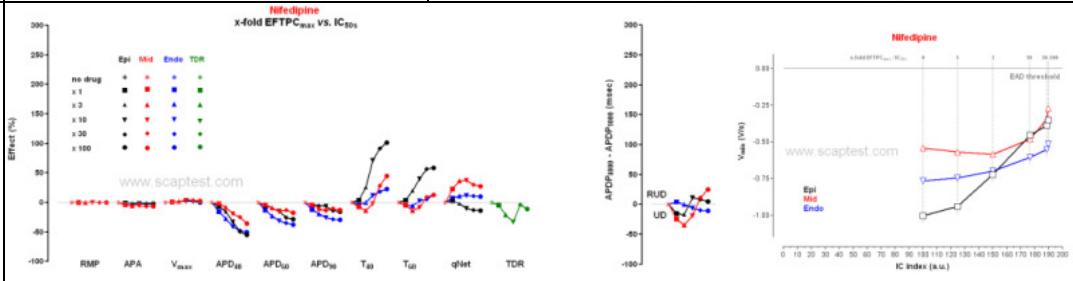


Reverse use dependence on midmyocardial myocytes

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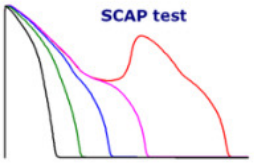
Abbreviations

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_{Ks}+I_{to}+I_{NaL}+I_{K1}, **RMP** : resting membrane potential, **RUD** : reverse use dependence, $T_{40,60}$: APD_{90}-APD_{40} or APD_{50} (^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

Nilotinib

Tyrosine kinase inhibitor used to treat chronic myeloid leukemia

Raw data

IC_{50s} (slope) (1)

I_{CaL} : 17.5 µM (1.0)
I_{Kr} : 1.0 µM (0.96)
I_{Na} : 13.3 µM (2.11)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ (1)

0.172 µM

TdP risk

Redfern (2) : not reported
Kramer (3) : torsadogenic (class 2)
CredibleMeds (4) : possible risk of TdP (class 2)
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}

$$I_j = g\,O\,(V - E_{ion})$$

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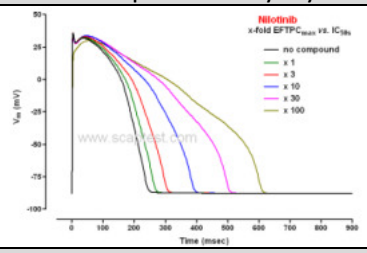
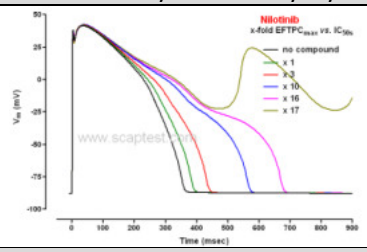
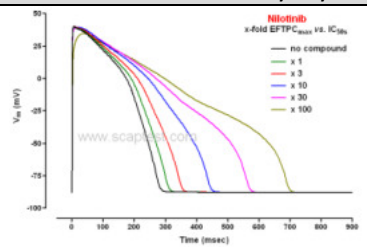
Human epicardial myocytes



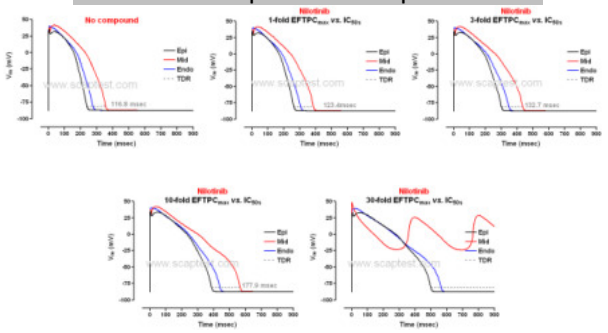
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarisation



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1 - CL 1000 msec without compound
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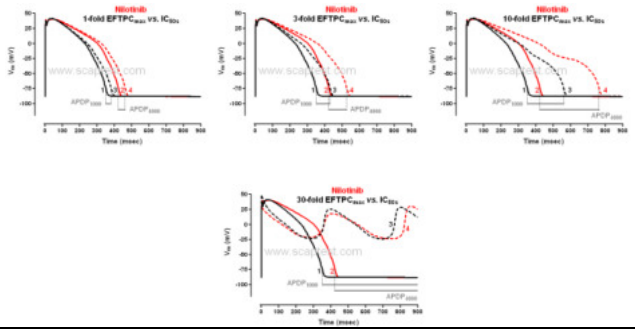
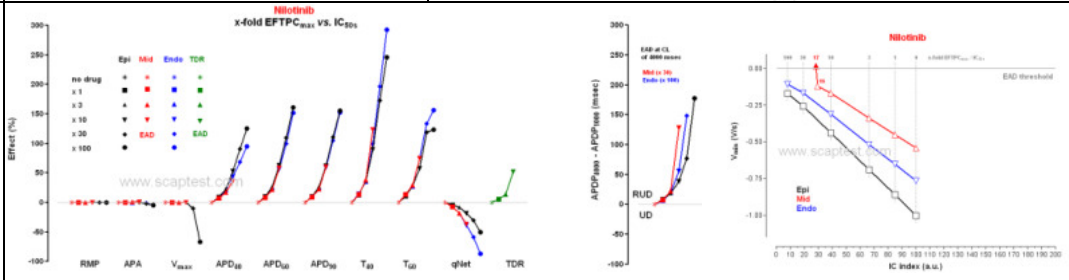


Summary



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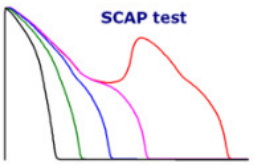

Drug

Nimodipine

Voltage-gated L-type Ca^{++} channel (Ca_v 1.2) blocker used to improve neurological outcomes in patients with subarachnoid hemorrhage

Raw data

IC_{50s} (slope) (1)

I_{CaL} : 0.139 µM (0.63)
I_{Kr} : 45.6 µM (1.0)
I_{Na} : ---- µM (---)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ (1)

0.001 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:
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- External ionic concentrations (mM): $[Na^+]_o$ 140 - $[Ca^{++}]_o$ 1.8 - $[K^+]_o$ 5.4
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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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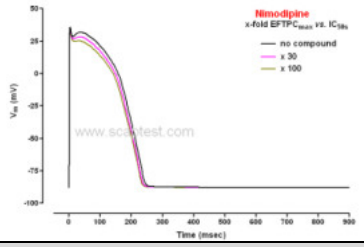
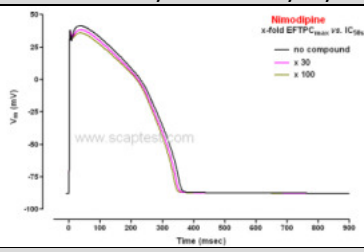
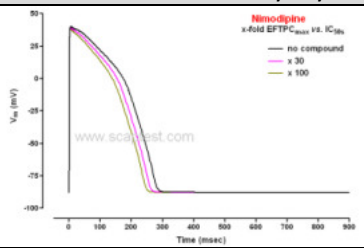
Human epicardial myocytes



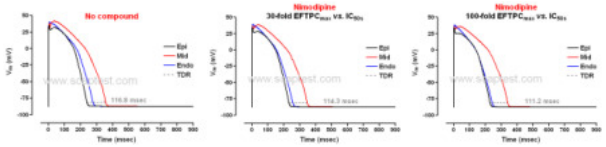
Human midmyocardial myocytes



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
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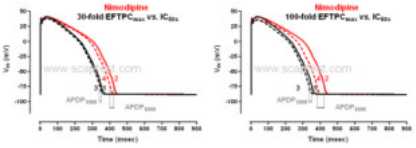
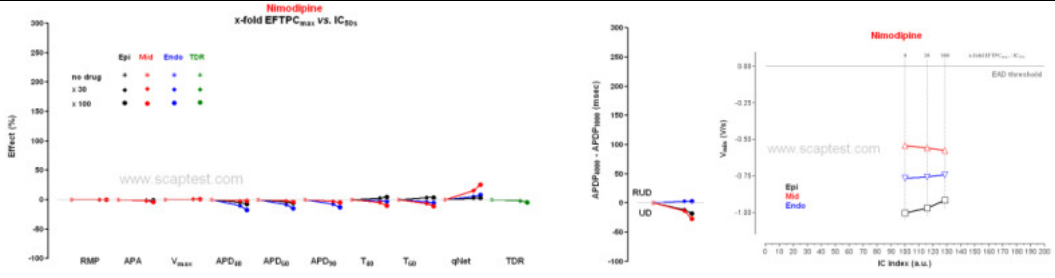


Summary



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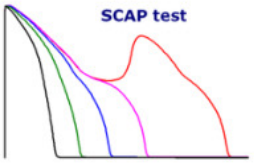
3. Kramer J et al. (2013) *Sci.rep.* **3** : 2100
4. Woosley RL (2015) www.CredibleMeds.org
5. CiPA (2016) www.elsiextra.org/hesi/science/cardiac/cipa/Project
6. Wiśniowska B et al. (2017) *Drug discovery today* **22** : 10-16
7. O'Hara T et al. (2011) *PLoS Comput. Biol.* **7** : e1002061_8
8. Mirams 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_{to}+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

Nisoldipine

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

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 0.079 µM (1.0)
I_{to} : ---- µM (---)
I_{Kr} : 22.91 µM (1.0)
I_{NaL} : ---- µM (---)
I_{Na} : ---- µM (---)
I_{K1} : ---- µM (---)
I_{Ks} : 39.81 µM (1.0)

$EFTPC_{max}$ [1]

0.0001 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
- 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:

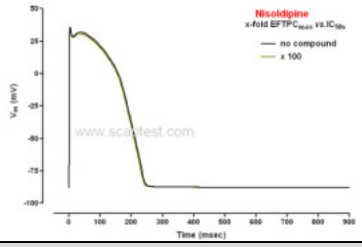
- TDR = APD_{90} mid - APD_{90} epi (at CL of 1000 msec)
- RUD = $APD_{90}P_{4000}$-$APD_{90}P_{1000}$

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

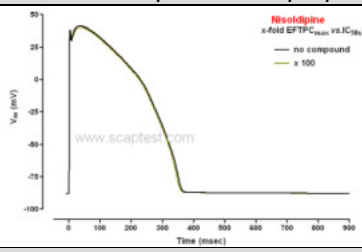
IC index calculation [9]:

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

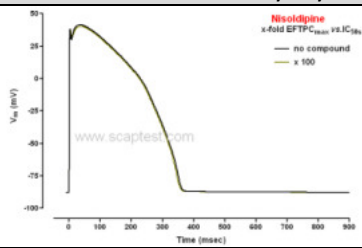
Human epicardial myocytes



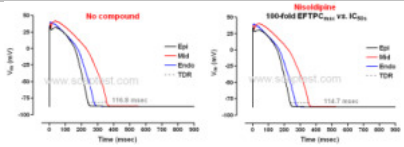
Human midmyocardial myocytes



Human endocardial myocytes

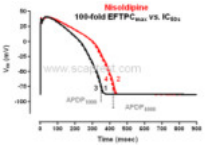


Transmural dispersion of repolarisation

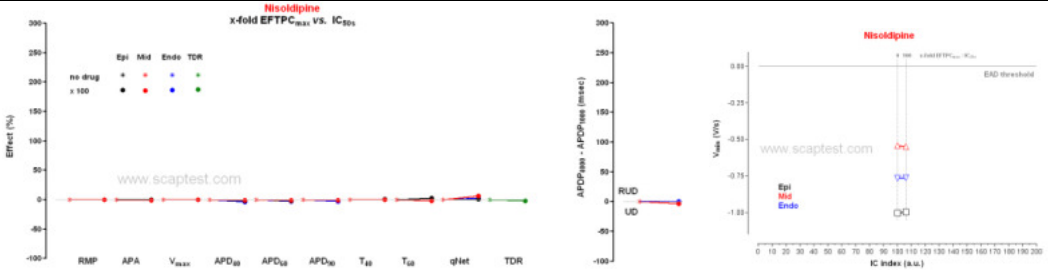


Reverse use dependence on midmyocardial myocytes

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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2. Redfern WS et al. (2003) *Cardiovasc. Res.* **58** : 32-45
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Abbreviations

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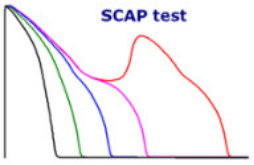

Drug

Nitrendipine

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

Raw data

IC_{50s} (slope) (1)

I_{CaL} : 0.025 µM (0.78)
I_{to} : ---- µM (---)
I_{Kr} : 24.6 µM (0.82)
I_{NaL} : ---- µM (---)
I_{Na} : 21.6 µM (1.25)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ (1)

0.003 µM

TdP risk

Redfern (2) : no published report of TdP (class 5)
Kramer (3) : non-torsadogenic (class 1)
CredibleMeds (4) : not reported
CiPA (5) : low risk or no risk of TdP (class 3)
WP (6) : 0/7 (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'
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where
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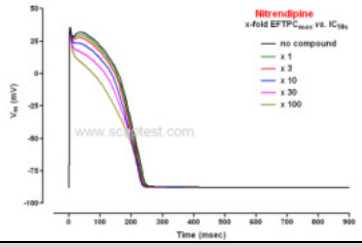
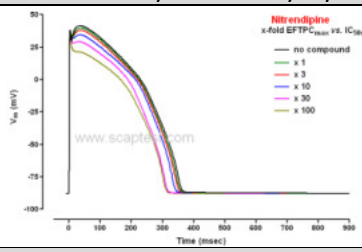
IC index calculation (9):

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

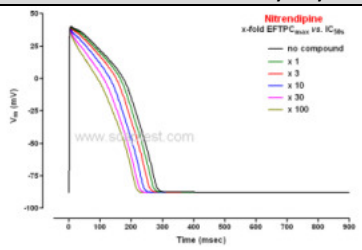
Human epicardial myocytes



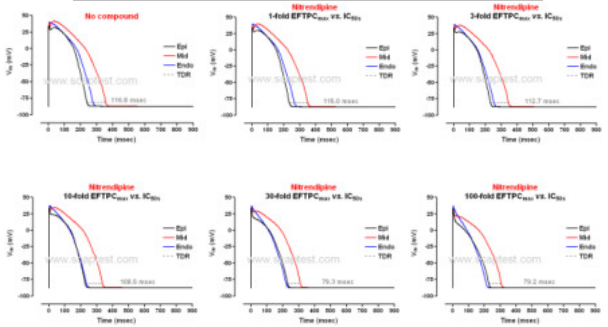
Human midmyocardial myocytes



Human endocardial myocytes

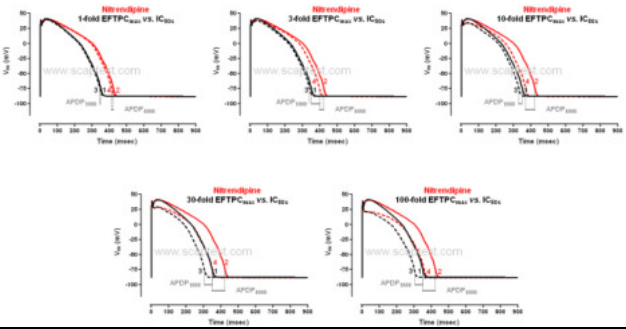


Transmural dispersion of repolarisation

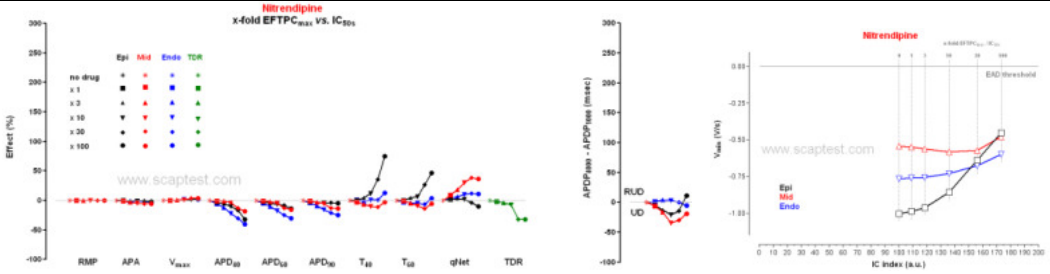


Reverse use dependence on midmyocardial myocytes

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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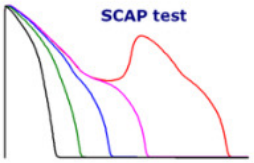


Drug

Ofloxacin

Quinolone/fluoroquinolone antibiotic used to treat various bacterial infections

Raw data

IC_{50s} (slope) [1]

I_{CaL} : ---- µM (---)
I_{to} : ---- µM (---)
I_{Kr} : 1412.5 µM (1.0)
I_{NaL} : ---- µM (---)
I_{Na} : ---- µM (---)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ [1]

8.656 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}

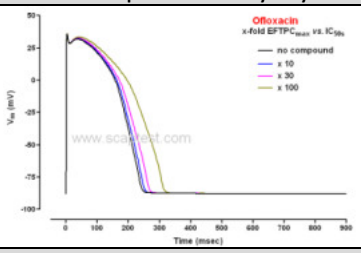
$I_j = g\,O\,(V - E_{ion})$ (g = maximal conductance of channel j; O = open probability of channel j; V = voltage membrane; E_{ion} = reversal potential for species of ions which flows through channel j)

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

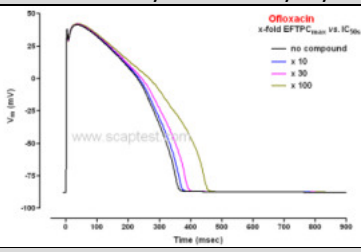
TDR and RUD estimation:
- TDR = APD_{90} mid - APD_{90} epi (at CL of 1000 msec)
- RUD = $APD_{90}P_{x000}$- $APD_{90}P_{1000}$ where $APD_{90}P_x$ = APD_{90} with - APD_{90} without compound at CL x

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}.

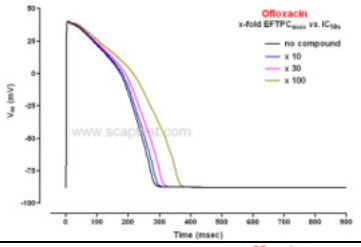
Human epicardial myocytes



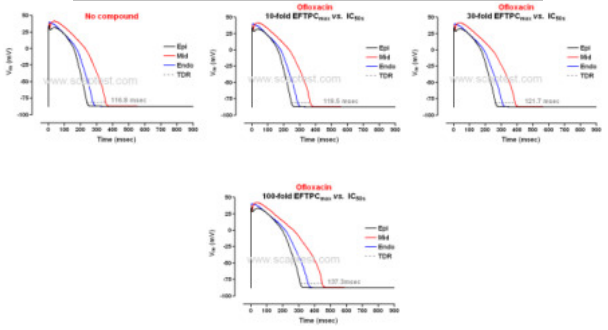
Human midmyocardial myocytes



Human endocardial myocytes

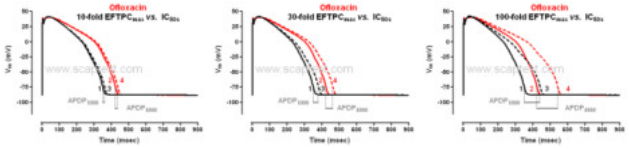


Transmural dispersion of repolarisation

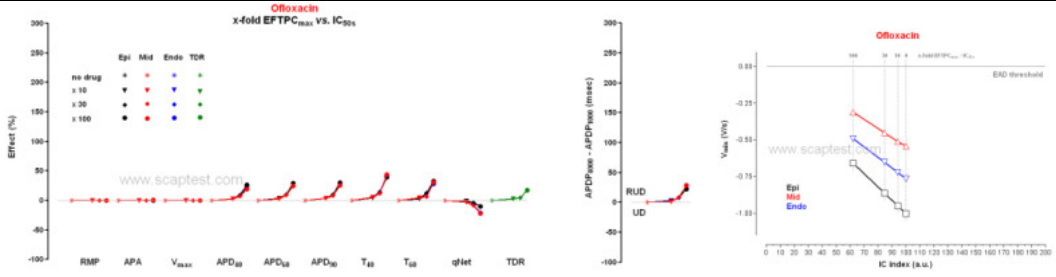


Reverse use dependence on midmyocardial myocytes

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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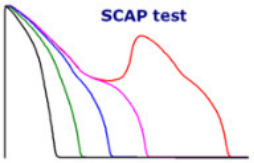

Drug

Olanzapine

Multiple neuronal receptor antagonist (dopaminergic, serotoninergic, adrenergic, histaminergic and muscarinic) used to treat schizophrenia and bipolar1 disorder

Raw data

IC_{50s} (slope) [1]

I_{CaL} : ---- µM (---)
I_{Kr} : 9.99 µM (1.23)
I_{Na} : 39.0 µM (1.0)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ [1]

13.63 µM

TdP risk

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

Results

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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}

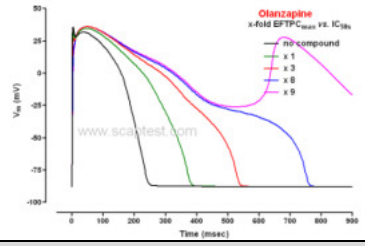
$I_j = g\,O\,(V - E_{ion})$ (g = maximal conductance of channel ; O = open probability of channel ; V = voltage membrane ; E_{ion} = reversal potential for species of ions which flows through channel)

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

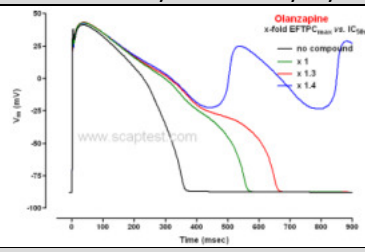
TDR and RUD estimation:
- TDR = APD_{90} mid - APD_{90} epi (at CL of 1000 msec)
- RUD = $APD_{90}P_{x000}$- $APD_{90}P_{1000}$ where $APD_{90}P_x$ = APD_{90} with - APD_{90} without compound at CL x

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}.

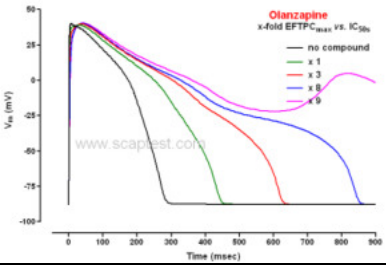
Human epicardial myocytes



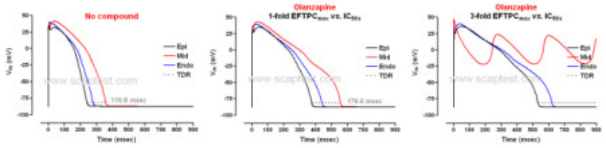
Human midmyocardial myocytes



Human endocardial myocytes

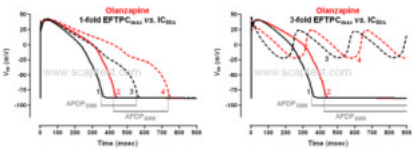


Transmural dispersion of repolarisation

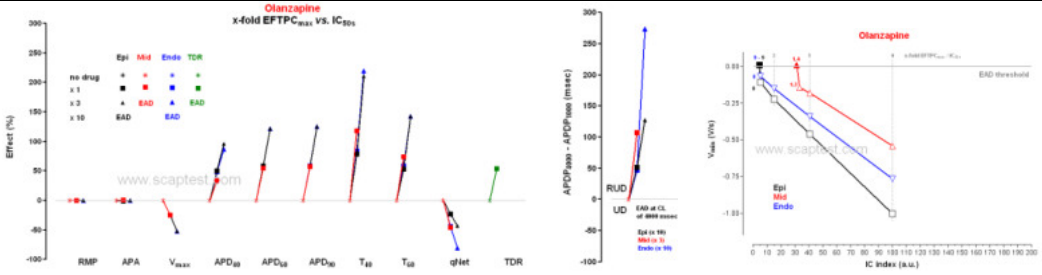


Reverse use dependence on midmyocardial myocytes

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
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6. Wiśniowska B et al. (2017) *Drug discovery today* **22** : 10-16
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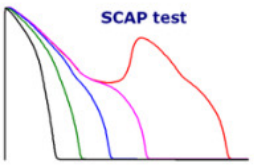
8. Mirams GR et al. (2011) *Cardiovasc. Res.* **91** : 53-61
9. Christophe B & Crumb WJ Jr (2019) *J Pharmacol Toxicol Methods* **96** : 15-26

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_{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	**Omecamtiv mecarbil** Myosin activator investigated to treat heart failure with reduced ejection fraction

Raw data

IC_{50s} (slope) [1]	$EFTPC_{max}$ [1]	TdP risk
I_{CaL} : 581.8 µM (1.0) I_{Kr} : 125.5 µM (1.1) I_{Na} : 400.4 µM (1.0) I_{Ks} : ---- µM (---) I_{to} : ---- µM (---) I_{NaL} : ---- µM (---) I_{K1} : ---- µM (---)	0.3 µM	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 = 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'

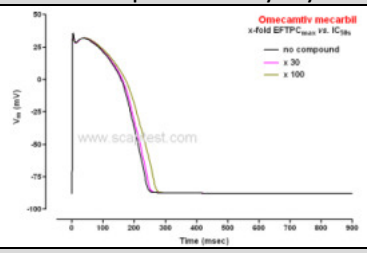
$g_j = g_{control,j}\left[1 + \left(\frac{D}{IC50_j}\right)^n\right]^{-1}$ g = maximal conductance of channel 'j' $g_{control,j}$= drug-free maximal conductance of channel 'j' IC50 = 50% of inhibition of a drug for channel 'j' D= drug concentration (EFTPC for example) n= hill slope

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

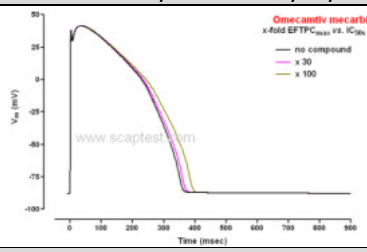
where
$APD_{90}P_x$ = APD_{90} with - APD_{90} without compound at CL x

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}

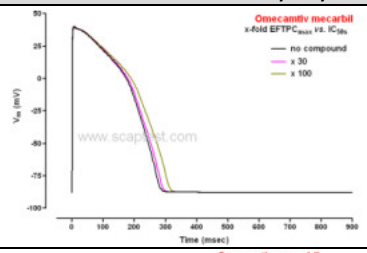
Human epicardial myocytes



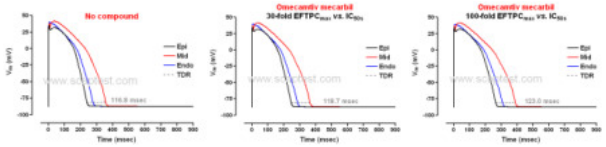
Human midmyocardial myocytes



Human endocardial myocytes

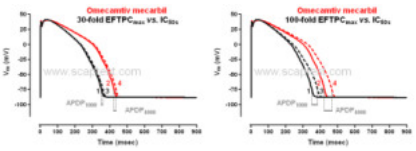


Transmural dispersion of repolarisation

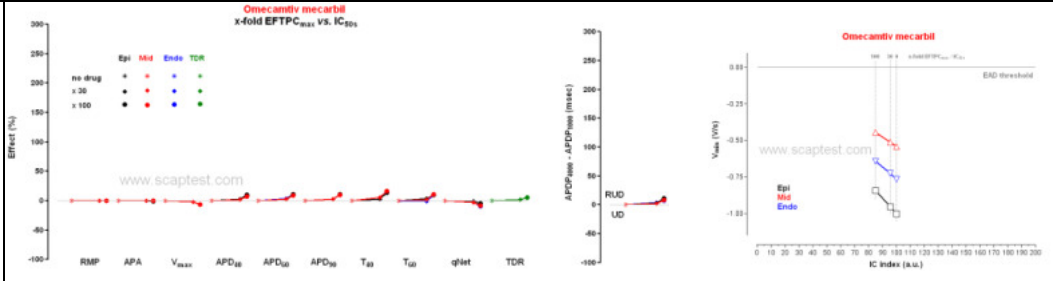


Reverse use dependence on midmyocardial myocytes

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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4. Woosley RL (2015) www.CredibleMeds.org
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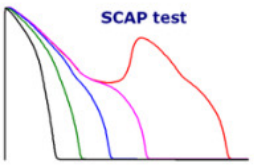
9. Christophe B & Crumb WJ Jr (2019) *J Pharmacol Toxicol Methods* **96** : 15-26

Abbreviations

AP : action potential, **APA** : AP amplitude, **$APD_{40, 60 or 90}$** : AP duration at 40, 60 or 90 % of APA, **APDP** : APD prolongation, **a.u.** : arbitrary unit, **CL** : cycle lenght , **DA** : depolarization abnormalities, **EAD** : early afterdepolarization, **EFTPCmax** : maximal effective free therapeutic plasma concentration, **endo** : endocardial myocyte, **epi** : epicardial myocyte, **IC index** : ion channel inhibition index, **IC_{50}** : 50% inhibition concentration, **mid** : midmyocardial myocyte, **msec** : millisecond, **mV** : millivolt, **qNet** : integration sum of I_{CaL}+I_{to}+I_{Na}+I_{NaL}+I_{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

Ondansetron

Serotonin 5-HT$_3$ recetor antagonist used to treat nausea and vomiting

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 22.551 µM (0.8)
I_{to} : ---- µM (---)
I_{Kr} : 1.492 µM (1.0)
I_{NaL} : 19.181 µM (1.0)
I_{Na} : ---- µM (---)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ [1]

0.3585 µM

TdP risk

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

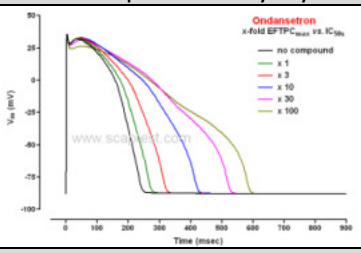
- TDR = APD_{90} mid - APD_{90} epi (at CL of 1000 msec)
- RUD = $APD_{90}P_{x400}$- $APD_{90}P_{1000}$

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

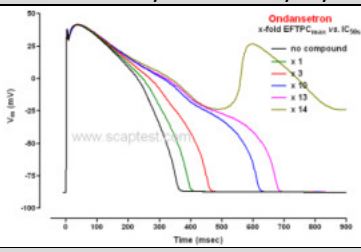
IC index calculation [9]:

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

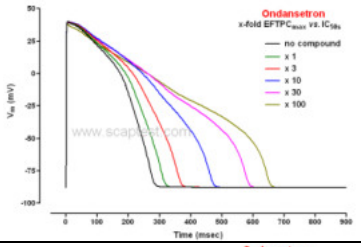
Human epicardial myocytes



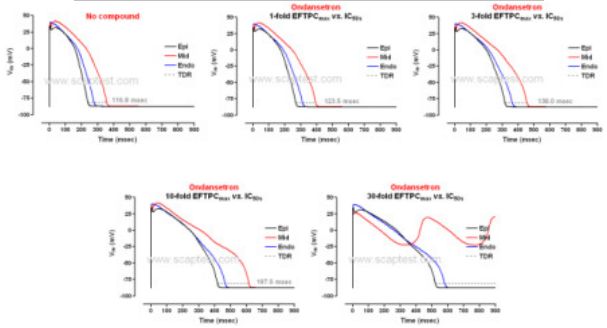
Human midmyocardial myocytes



Human endocardial myocytes

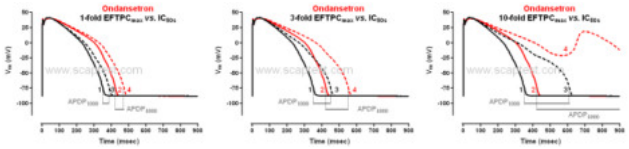


Transmural dispersion of repolarisation

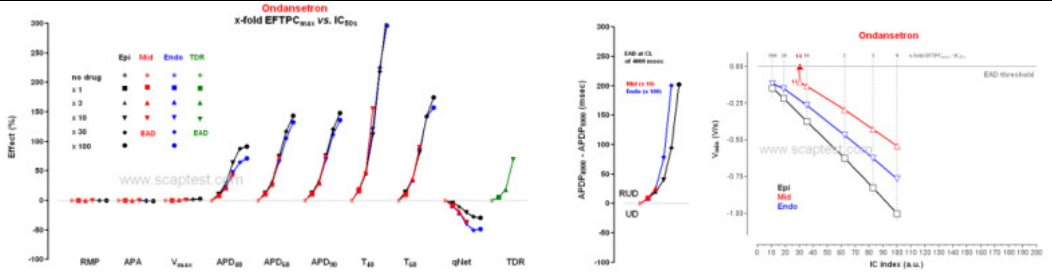


Reverse use dependence on midmyocardial myocytes

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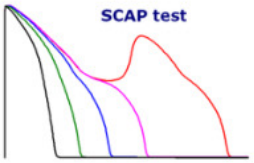

Drug

Oxybutynin

Muscarinic M_1, M_2 and M_3 receptor antagonist used to treat urinary incontinence

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 16.1 µM (0.95)
I_{to} : ---- µM (--)
I_{Kr} : 11.4 µM (1.0)
I_{NaL} : ---- µM (--)
I_{Na} : ---- µM (--)
I_{K1} : 18.2 µM (1.0)
I_{KS} : 28.7 µM (0.87)

$EFTPC_{max}$ [1]

0.00005 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}

$I_j = g\,O\,(V - E_{ion})$ (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= fold slope)

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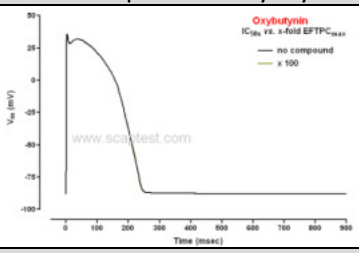
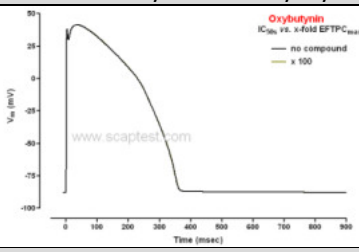
IC index = (AFKr/((AFNaL+AFCaL)/2))*100
where
AFKr, AFNaL and AFCaL = active fraction (%) of the I_{Ks}, I_{NaL} and I_{CaL}.

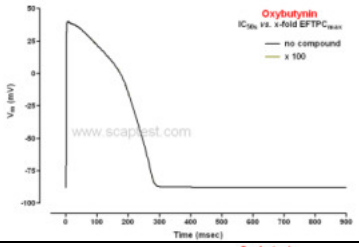
Human epicardial myocytes



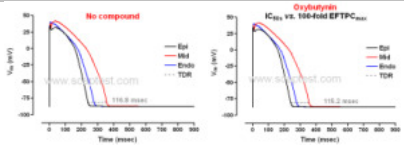
Human midmyocardial myocytes



Human endocardial myocytes

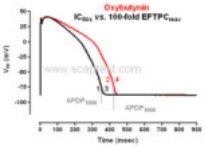


Transmural dispersion of repolarisation

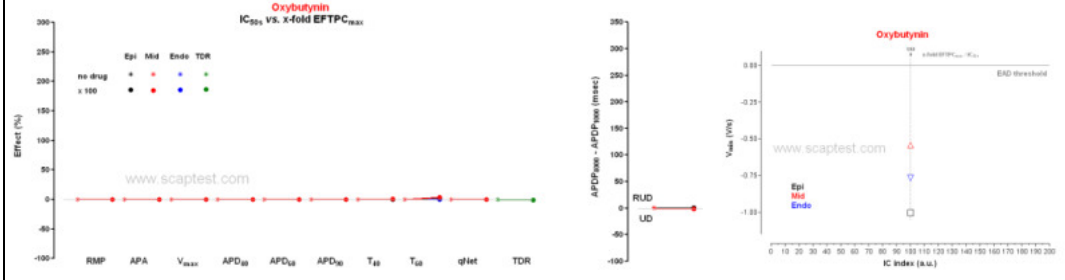


Reverse use dependence on midmyocardial myocytes

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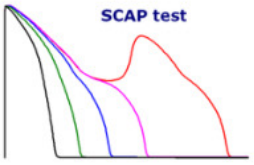
8. Mirams GR et al. (2011) *Cardiovasc. Res.* **91** : 53-61
9. Christophe B & Crumb WJ Jr (2019) *J Pharmacol Toxicol Methods* **96** : 15-26

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_{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

Paliperidone

Dopamine D_2 and serotonin 5-HT_2 receptor antagonist used to treat schizophrenia

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 193.9 µM (1.0)
I_{to} : ---- µM (---)
I_{Kr} : 0.78 µM (1.01)
I_{NaL} : ---- µM (---)
I_{Na} : 109.0 µM (1.33)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ [1]

0.069 µM

TdP risk

Redfern [2] : not reported
Kramer [3] : torsadogenic (class 2)
CredibleMeds [4] : possible risk of TdP (class 2)
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}

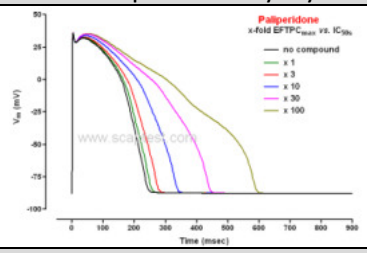
$I_j = g_j O(V - E_{ion})$ g = maximal conductance of channel 'j' O=open probability of channel 'j' V= voltage membrane E_{ion}= reversal potential for species of ions which flows through channel 'j'

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

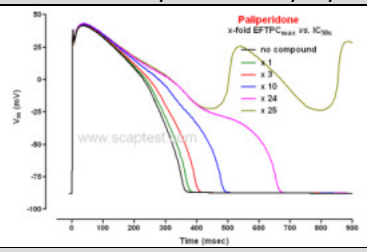
TDR and RUD estimation:
- TDR = APD_{90} mid - APD_{90} epi (at CL of 1000 msec)
- RUD = $APD_{90}P_{4000}$-$APD_{90}P_{1000}$ where $APD_{90}P_x$ = APD_{90} with - APD_{90} without compound at CL x

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}.

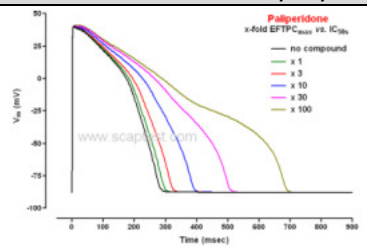
Human epicardial myocytes



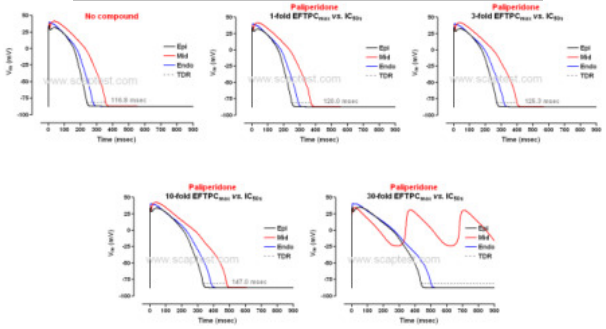
Human midmyocardial myocytes



Human endocardial myocytes

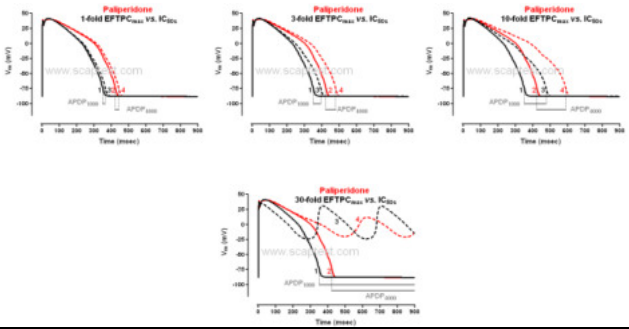


Transmural dispersion of repolarisation

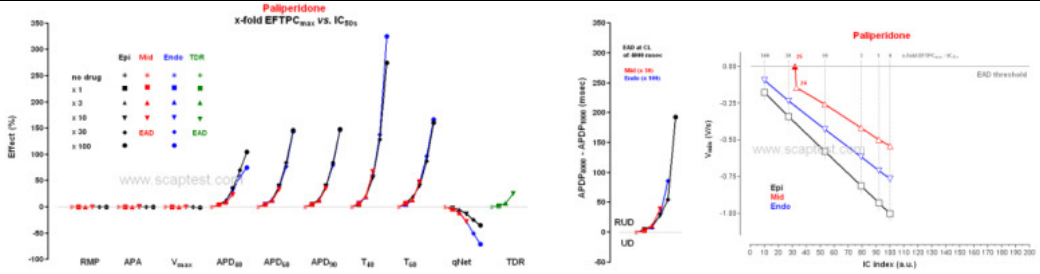


Reverse use dependence on midmyocardial myocytes

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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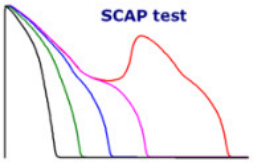

Drug

Palonosetron

Serotonin 5-HT$_3$ receptor antagonist used to treat vomiting and nausea

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 398.107 µM (1.0)
I_{Kr} : 1.995 µM (1.0)
I_{Na} : 19.953 µM (1.0)
I_{Ks} : 50.119 µM (1.0)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ [1]

0.004651 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'

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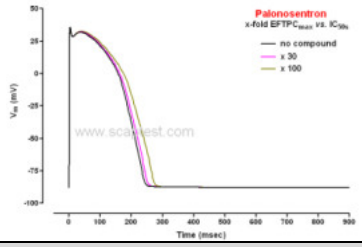
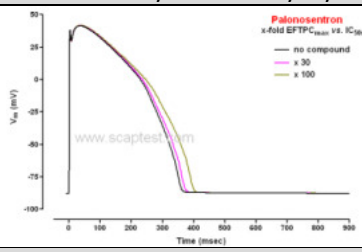
where
$APD_{90}P_x$ = APD_{90} with - APD_{90} without compound at CL x

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}

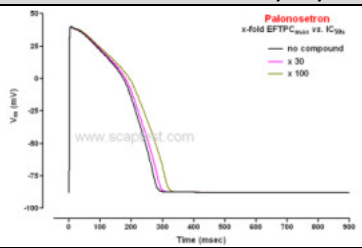
Human epicardial myocytes



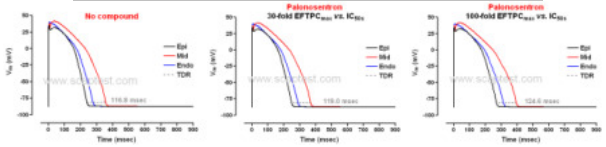
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarisation



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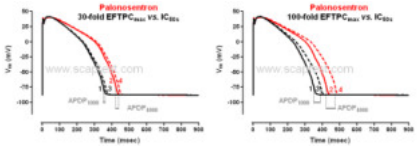
1 - CL 1000 msec without compound
2 - CL 4000 msec without compound
3 - CL 1000 msec with compound
4 - CL 4000 msec with compound



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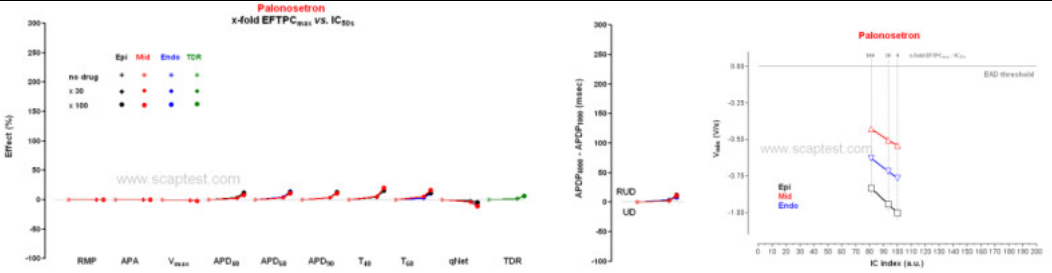

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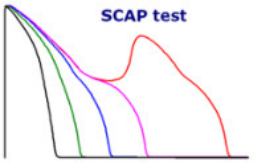

Drug

Paroxetine

5-HT reuptake inhibitor used to treat depressive, anxiety, panic, obsessive compulsive or premenstrual dysphoric disorders and social phobia

Raw data

IC_{50s} (slope) (1)

I_{CaL} : 3.9 µM (1.39)
I_{Kr} : 1.9 µM (1.26)
I_{Na} : 9.8 µM (1.34)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ (1)

0.014 µM

TdP risk

Redfern (2) : not reported
Kramer (3) : torsadogenic (class 2)
CredibleMeds (4) : conditional risk of TdP (class 3)
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 = 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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IC index = (AFKr/((AFNaL+AFCaL)/2))*100
where
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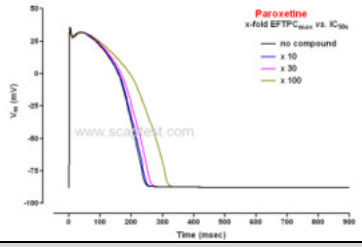
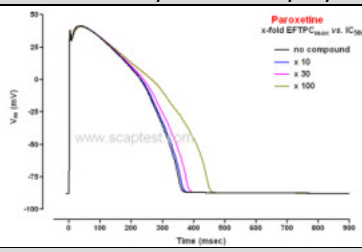
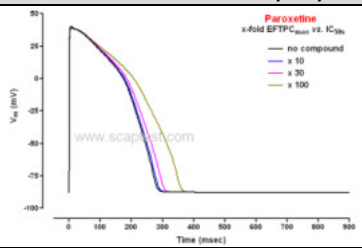
Human epicardial myocytes



Human midmyocardial myocytes



Human endocardial myocytes



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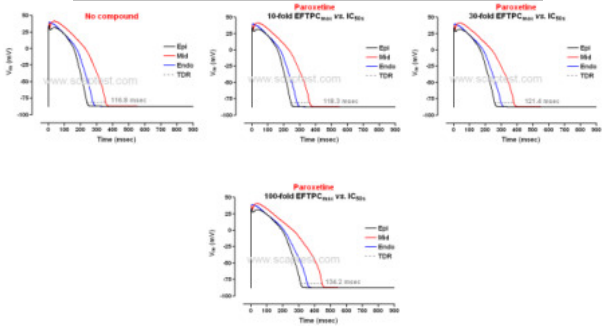

Reverse use dependence on midmyocardial myocytes

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2 - CL 4000 msec without compound
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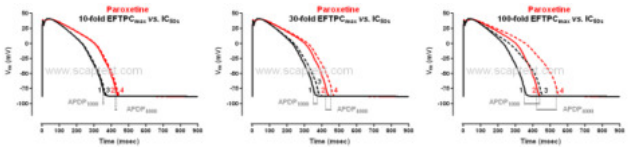

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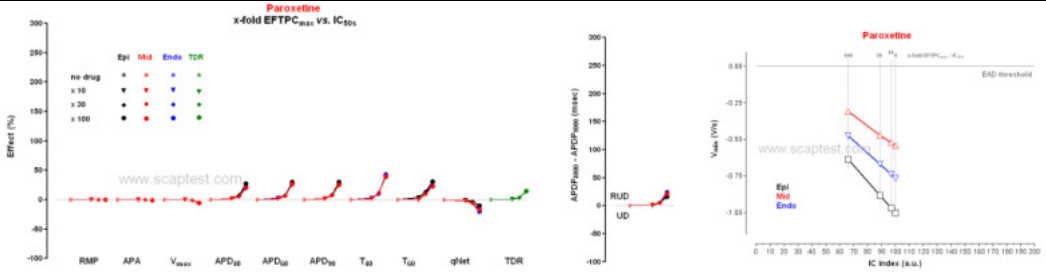

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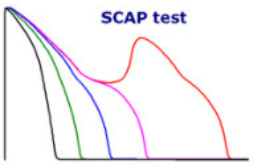

Drug

Pentamidine

Mechanism of action not fully understood, antifungal used to treat pneumonia in HIV patient

Raw data

IC_{50s} (slope) [1]

I_{CaL} : ---- µM (---)
I_{to} : ---- µM (---)
I_{Kr} : 205.02 µM (1.0)
I_{NaL} : ---- µM (---)
I_{Na} : ---- µM (---)
I_{K1} : 0.170 µM (1.0)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ [1]

0.010 µM

TdP risk

Redfern [2] : numerous reports of TdP (class 3)
Kramer [3] : not reported
CredibleMeds [4] : known risk of TdP (class 1)
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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'
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E_{ion} = reversal potential for species of ions which flows through channel 'j'

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g_j = maximal conductance of channel 'j'
$g_{control,j}$ = drug free maximal conductance of 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)
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where
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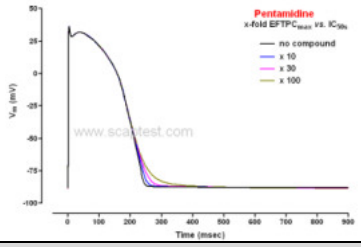
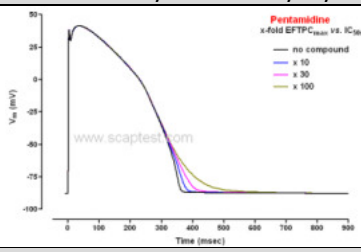
IC index calculation [9]:

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

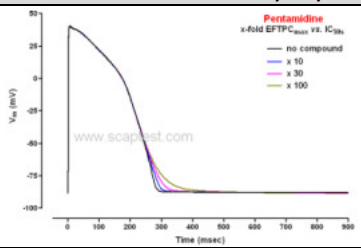
Human epicardial myocytes



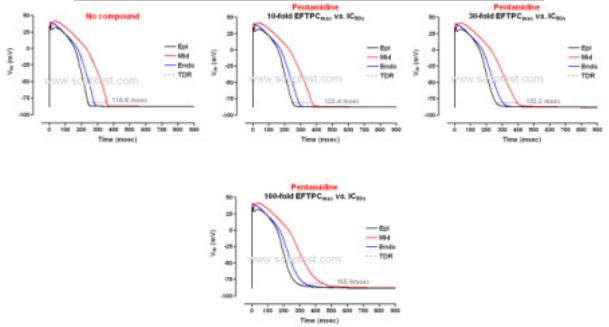
Human midmyocardial myocytes



Human endocardial myocytes

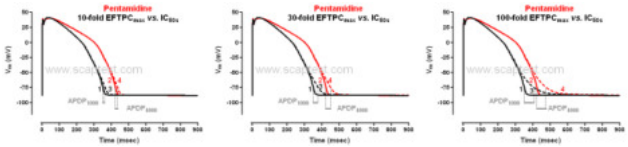


Transmural dispersion of repolarisation

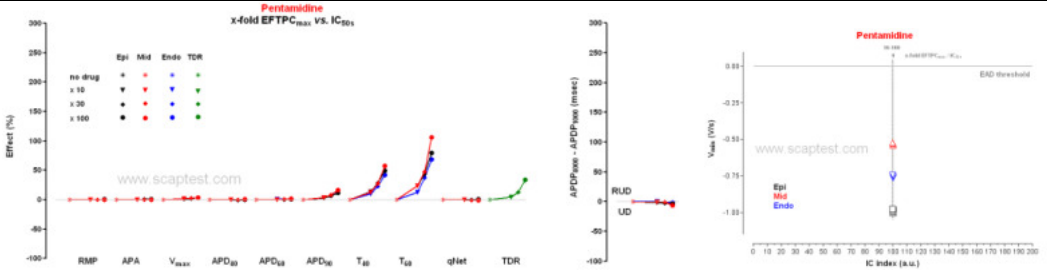


Reverse use dependence on midmyocardial myocytes

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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Abbreviations

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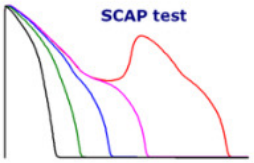

Drug

Pentobarbital

GABA$_A$ allosteric modulator used as barbiturate to treat seizure, cause sedation and induce sleep
no longer marketed in Sweden (Onakpoya et al (2016) *BMC Med.* **14**: 10)

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 299.0 µM (1.38)
I_{Kr} : 1433.9 µM (1.0)
I_{Na} : 2686.0 µM (1.0)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ [1]

5.171 µM

TdP risk

Redfern [2] : not reported
Kramer [3] : non-torsadogenic (class 1)
CredibleMeds [4] : not reported
CiPA [5] : not reported
WP [6] : 0/3 (TdP+/TdP-)

Results

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

Simulation conditions:

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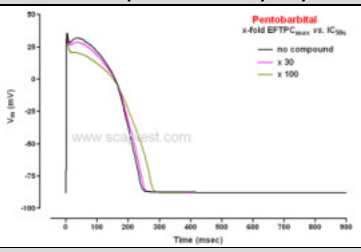
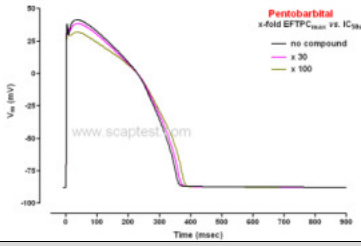
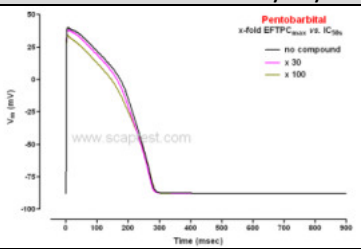
Human epicardial myocytes



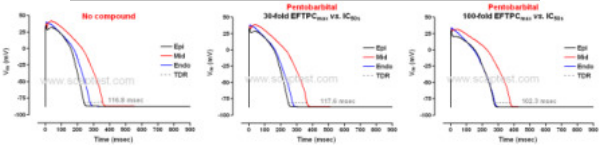
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarisation



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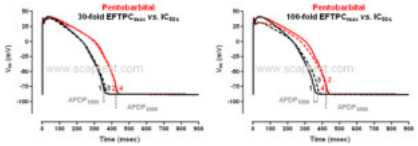
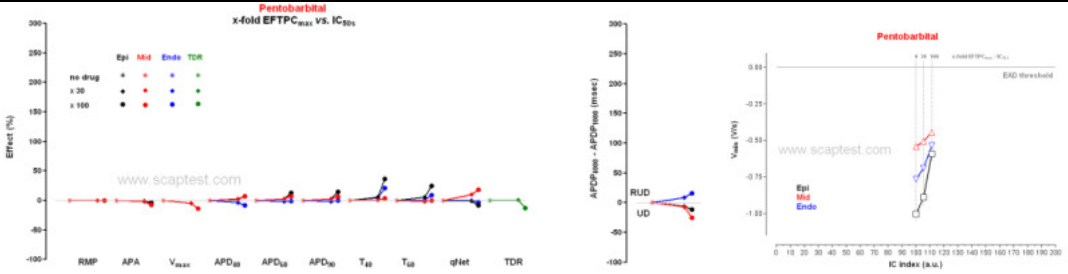


Summary



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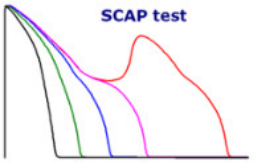

Drug

Phenytoin

Non-specific voltage-gated Na^+ channel blocker used as anticonvulsant to treat seizure

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 21.9 µM (0.99)
I_{to} : ---- µM (---)
I_{Kr} : 147.0 µM (1.0)
I_{NaL} : ---- µM (---)
I_{Na} : 72.4 µM (1.06)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ [1]

4.36 µM

TdP risk

Redfern [2] : no published report of TdP (class 5)
Kramer [3] : non-torsadogenic (class 1)
CredibleMeds [4] : not classified with TdP risk (class 4)
CiPA [5] : not reported
WP [6] : 0/5 (TdP+/TdP-)

Results

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

Simulation conditions:

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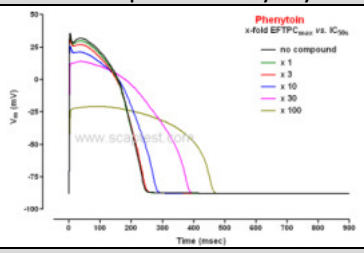
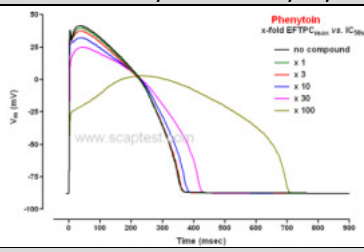
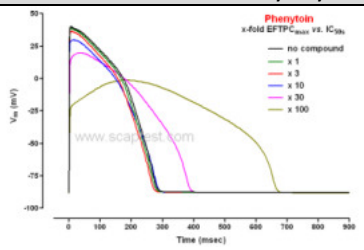
Human epicardial myocytes



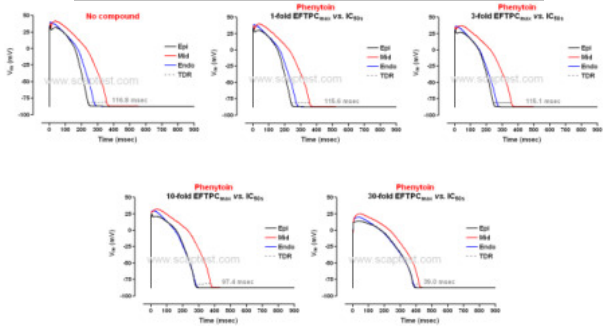
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarisation



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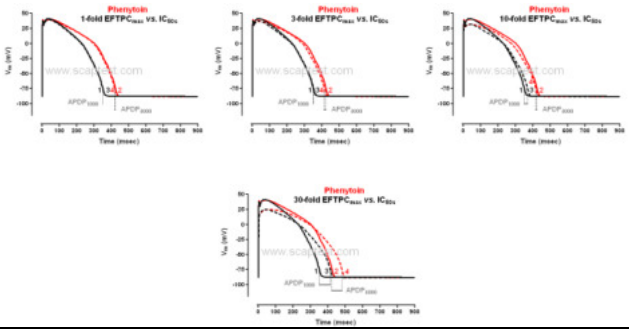

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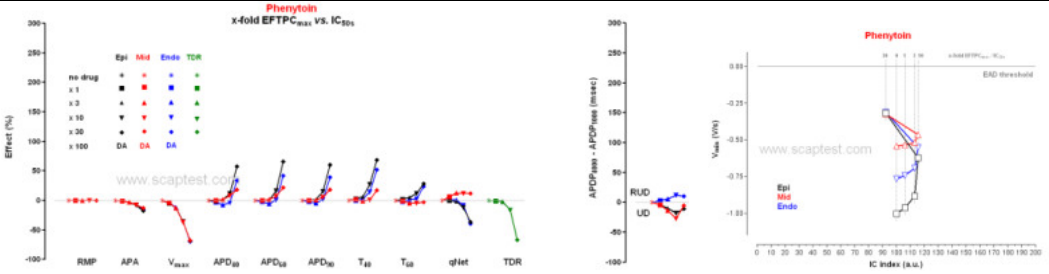

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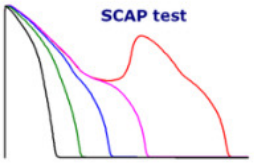

Drug

Pimozide

Dopamine D_2 receptor antagonist used to treat debilitating motor and phonic tics in Tourette's disorder

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 0.24 µM (1.49)
I_{Kr} : 0.04 µM (1.16)
I_{Na} : 1.1 µM (1.05)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ [1]

0.0005 µM

TdP risk

Redfern [2] : numerous reports of TdP (class 3)
Kramer [3] : torsadogenic (class 2)
CredibleMeds [4] : known risk of TdP (class 1)
CiPA [5] : intermediate risk of TdP (class 2)
WP [6] : 12/0 (TdP+/TdP-)

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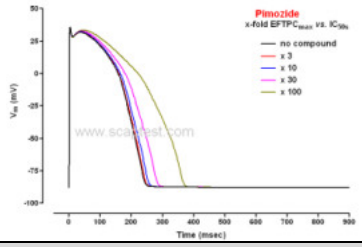
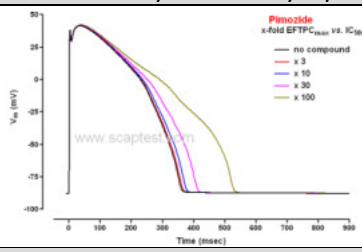
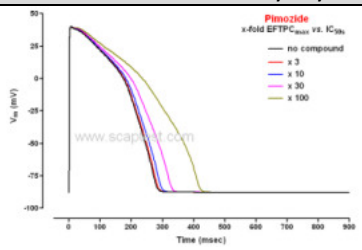


Human midmyocardial myocytes



Human endocardial myocytes



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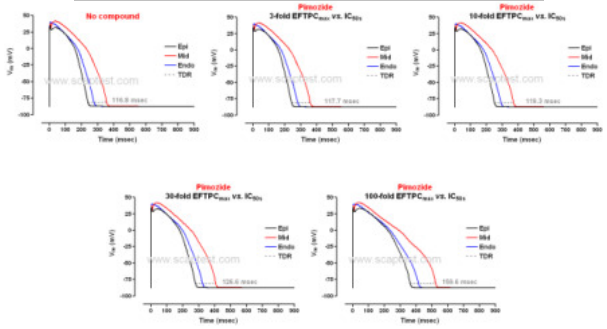
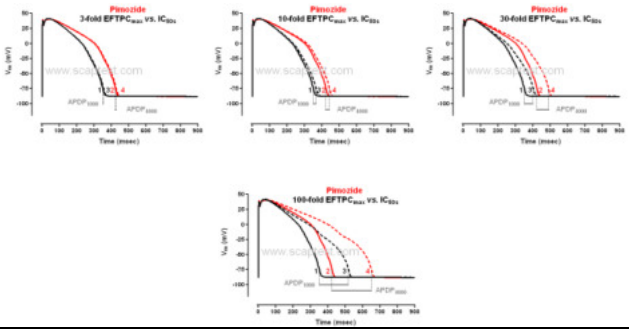
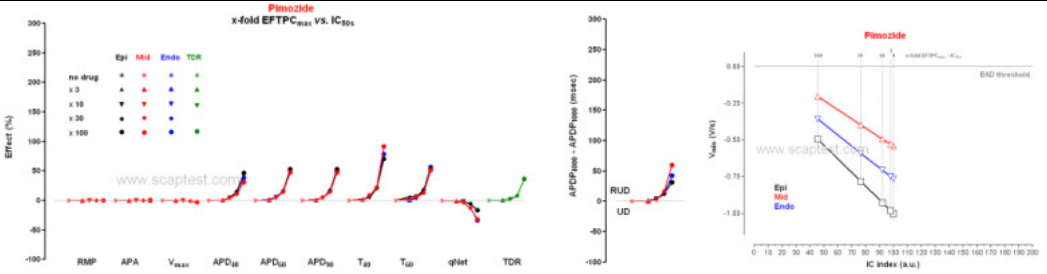


Reverse use dependence on midmyocardial myocytes

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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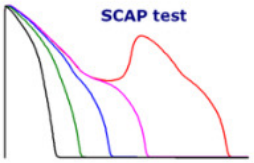
Abbreviations

AP : action potential, **APA** : AP amplitude, **$APD_{40, 60 or 90}$** : 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

Piperacillin

Penicillin antibiotic used to treat various bacterial infections

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 1226.0 µM (1.0)
I_{to} : ---- µM (---)
I_{Kr} : 3405.1 µM (1.0)
I_{NaL} : ---- µM (---)
I_{Na} : 2433.8 µM (1.0)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ [1]

1378.0 µM

TdP risk

Redfern [2] : not reported
Kramer [3] : non-torsadogenic (class 1)
CredibleMeds [4] : conditional risk of TdP (class 3)
CiPA [5] : not reported (+tazobactam)
WP [6] : 0/4 (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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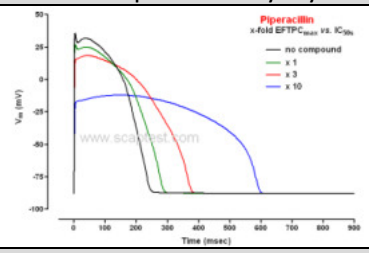
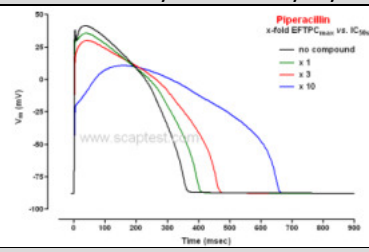
IC index calculation [9]:

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

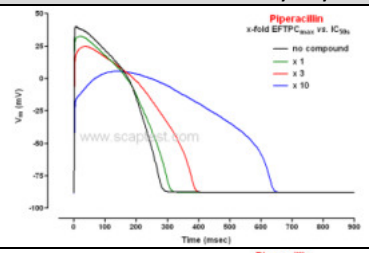
Human epicardial myocytes



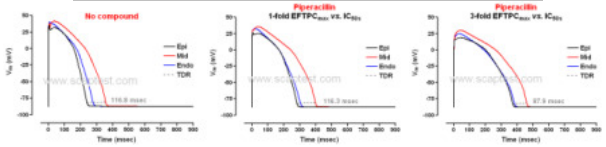
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarisation



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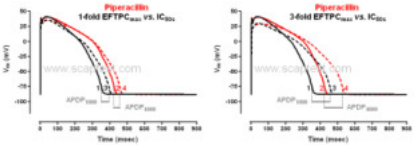

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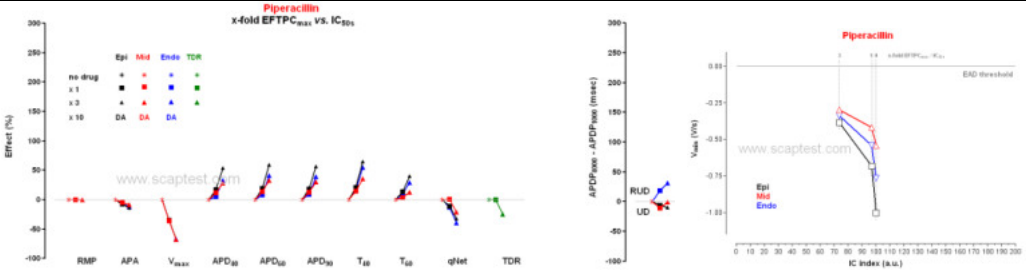

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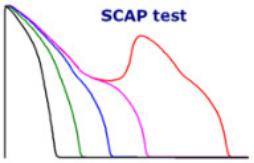

Drug

Prenylamine

Voltage-gated Ca^{++} channel ($Ca_v1.2$) blocker used to treat angina
no longer marketed worldwide (Onakpoya et al (2016) *BMC Med.* **14**: 10)

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 1.24 µM (1.0)
I_{Kr} : 0.065 µM (1.0)
I_{Na} : 2.52 µM (1.0)
I_{Ks} : 0.0 µM (---)
I_{to} : 0.0 µM (---)
I_{NaL} : 0.0 µM (---)
I_{K1} : 0.0 µM (---)

$EFTPC_{max}$ [1]

0.0035 µM

TdP risk

Redfern [2] : unacceptable risk of TdP (class 2)
Kramer [3] : not reported
CredibleMeds [4] : not reported
CiPA [5] : not reported
WP [6] : 7/0 (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'
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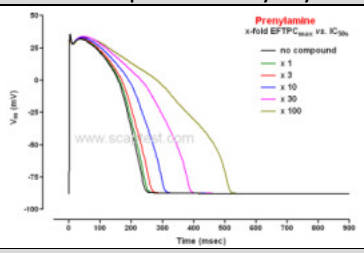
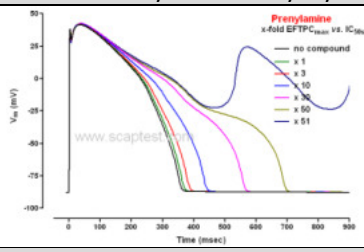
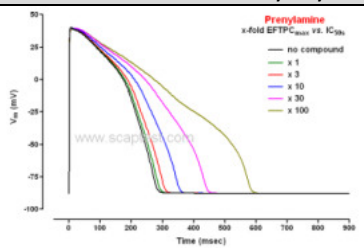
Human epicardial myocytes



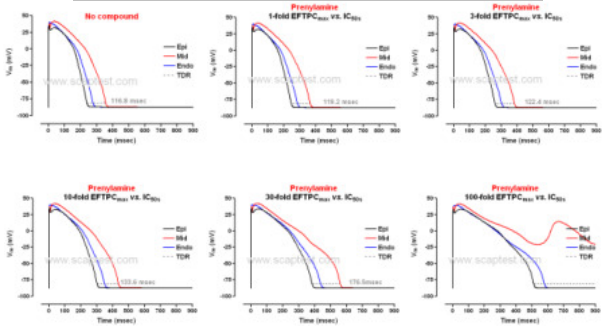
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarisation



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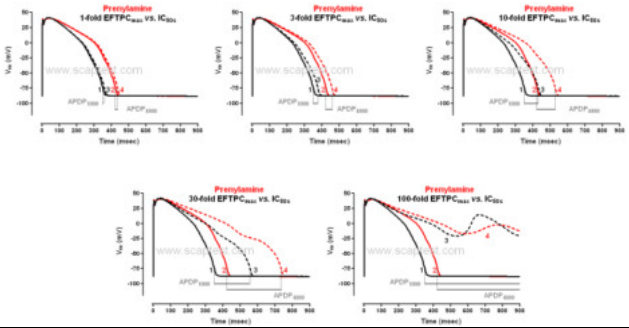

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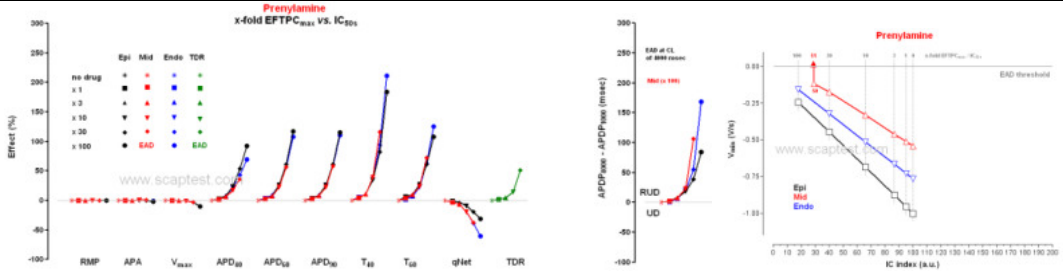

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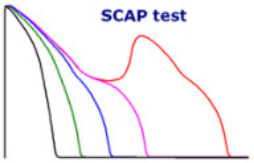

Drug

Primidone

Transmembrane Na^+ and Ca^{++} channel transport (TRPM3) blocker used to treat grand mal, psychomotor and focal epileptic seizures

Raw data

IC_{50s} (slope) [1]

I_{CaL} : ---- µM (---)
I_{Kr} : 3360 µM (1.0)
I_{Na} : 640 µM (1.0)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ [1]

20.6 µM

TdP risk

Redfern [2] : not reported
Kramer [3] : not reported
CredibleMeds [4] : not reported
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}

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

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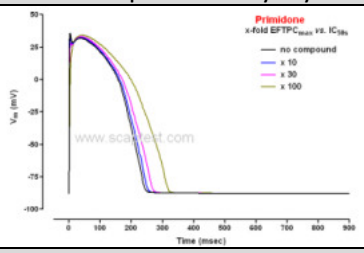
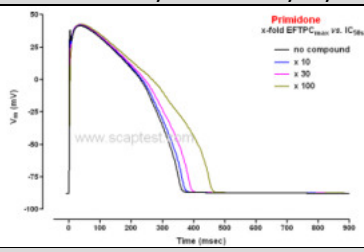
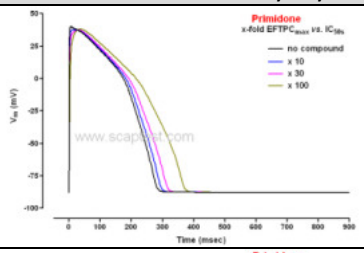
Human epicardial myocytes



Human midmyocardial myocytes



Human endocardial myocytes



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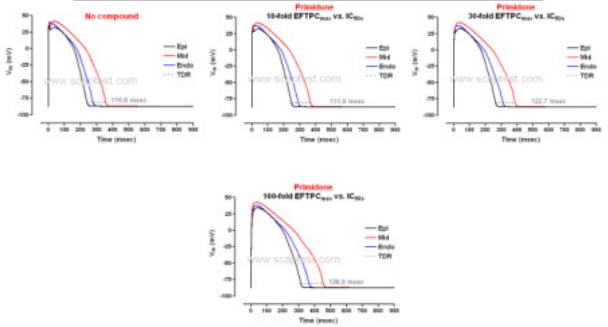

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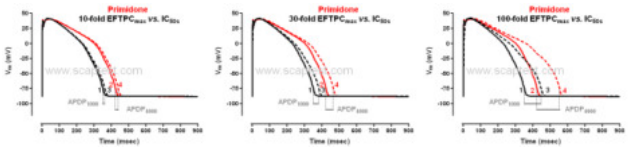

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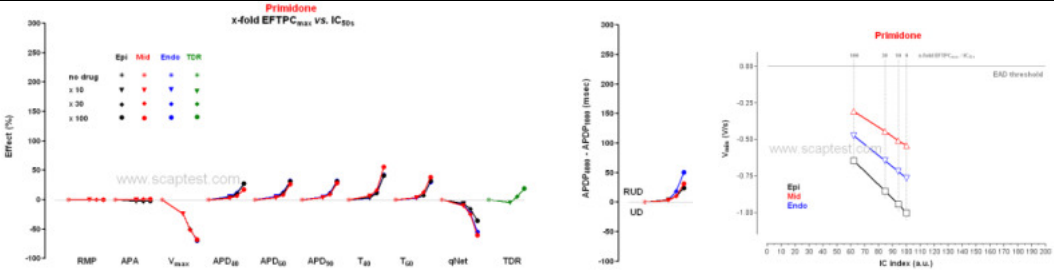

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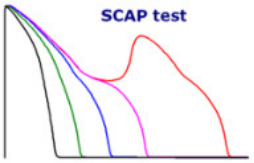


Drug

Procainamide

Voltage-gated Na^+ channel blocker used as class IA antiarrhythmic to treat ventricular arrhythmias

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 389.5 µM (0.83)
I_{Kr} : 272.4 µM (1.0)
I_{Na} : 746.6 µM (1.0)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ [1]

54.18 µM

TdP risk

Redfern [2] : class IA or III antiarrhythmics (class 1)
Kramer [3] : torsadogenic (class 2)
CredibleMeds [4] : known risk of TdP (class 1)
CiPA [5] : not reported
WP [6] : 9/0 (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}

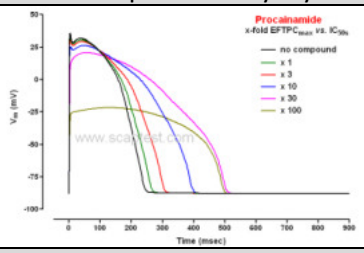
$I_j = g_j O(V - E_{ion})$ (g = maximal conductance of channel 'j' ; O=open probability of channel 'j' ; V= voltage membrane ; E_{ion} = reversal potential for species of ions which flows through channel 'j')

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

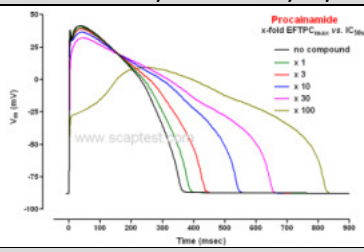
TDR and RUD estimation:
- TDR = APD_{90} mid - APD_{90} epi (at CL of 1000 msec)
- RUD = $APD_{90}P_{4000}$-$APD_{90}P_{1000}$ where $APD_{90}P_x$ = APD_{90} with - APD_{90} without compound at CL x

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}

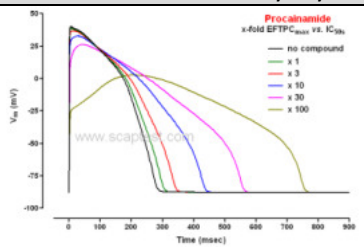
Human epicardial myocytes



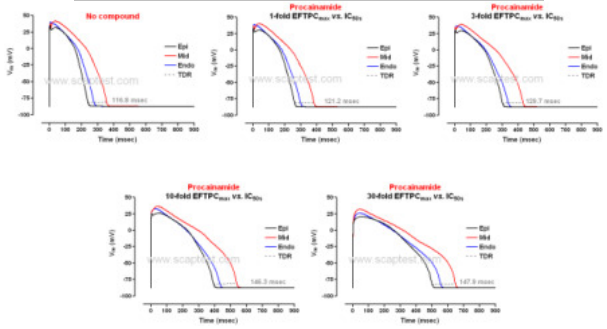
Human midmyocardial myocytes



Human endocardial myocytes

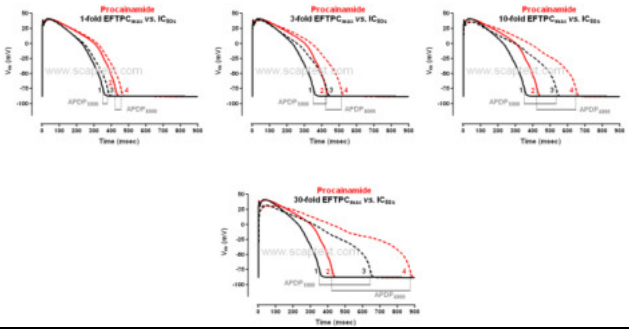


Transmural dispersion of repolarisation

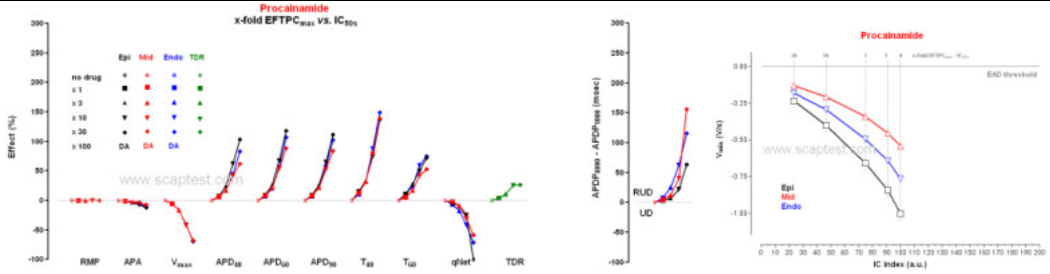


Reverse use dependence on midmyocardial myocytes

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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3. Kramer J et al. (2013) *Sci.rep.* **3** : 2100
4. Woosley RL (2015) www.CredibleMeds.org
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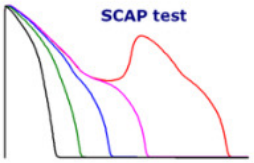
6. Wiśniowska B et al. (2017) *Drug discovery today* **22** : 10-16
7. O'Hara T et al. (2011) *PLoS Comput. Biol.* **7** : e1002061_8
8. Mirams GR et al. (2011) *Cardiovasc. Res.* **91** : 53-61
9. Christophe B & Crumb WJ Jr (2019) *J Pharmacol Toxicol Methods* **96** : 15-26

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

Propafenone

Voltage-gated Na^+ channel blocker and β-adrenocetptor antagonist used as class IC antiarrhythmic to treat ventricular arrhythmia and paroxysmal atrial fibrillation

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 1.55 µM (0.9)
I_{to} : ---- µM (---)
I_{Kr} : 0.481 µM (0.8)
I_{NaL} : 4.036 µM (0.9)
I_{Na} : 3.886 µM (0.9)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ [1]

0.131 µM

TdP risk

Redfern [2] : isolated reports of TdP (class 4)
Kramer [3] : not reported
CredibleMeds [4] : conditional risk of TdP (class 3)
CiPA [5] : not reported
WP [6] : 5/4 (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'
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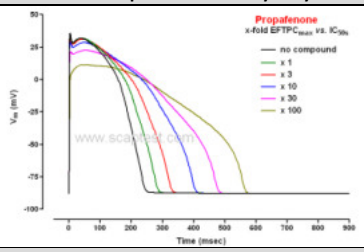
TDR and RUD estimation:
- TDR = APD_{90} mid - APD_{90} epi (at CL of 1000 msec)
- RUD = $APD_{90}P_{4000}$-$APD_{90}P_{1000}$

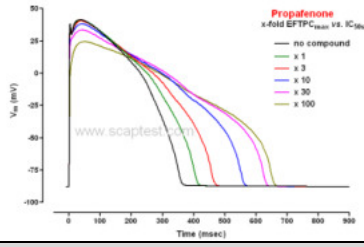
where
$APD_{90}P_x$ = APD_{90} with - APD_{90} without compound at CL x

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}.

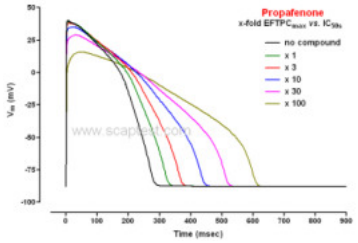
Human epicardial myocytes



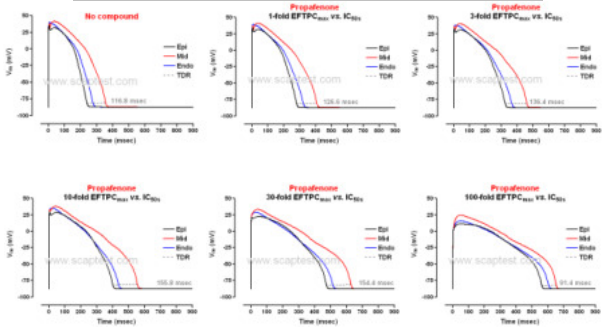
Human midmyocardial myocytes



Human endocardial myocytes

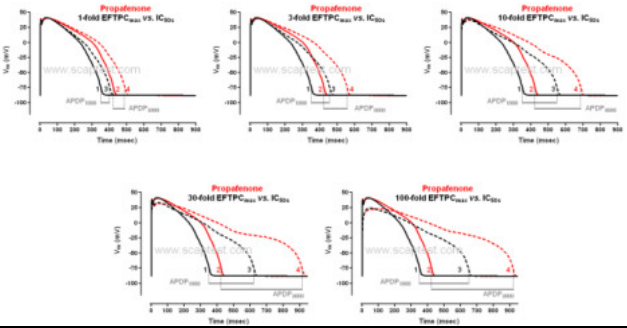


Transmural dispersion of repolarisation

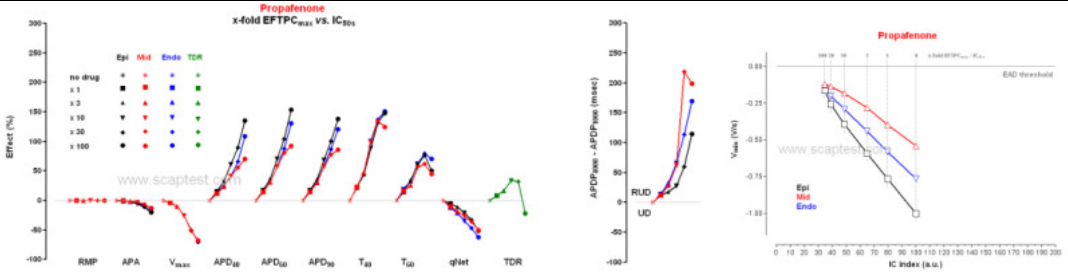


Reverse use dependence on midmyocardial myocytes

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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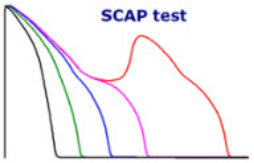
Abbreviations

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_{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

Propranolol

β-adrenoceptor antagonist used to treat hypertension, angina, atrial fibrillation, myocardial infarction, migraine or essential tremor

Raw data

IC_{50s} (slope) (1)

I_{CaL} : 19.498 µM (1.0)
I_{to} : ---- µM (---)
I_{Kr} : 8.128 µM (1.0)
I_{NaL} : ---- µM (---)
I_{Na} : ---- µM (---)
I_{K1} : ---- µM (---)
I_{Ks} : 1000.0 µM (1.0)

$EFTPC_{max}$ (1)

0.0101 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) : 0/4 (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}

$$I_j = g\,O\,(V - E_{ion})$$

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)
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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
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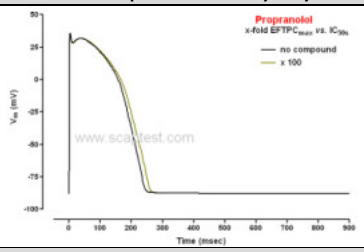
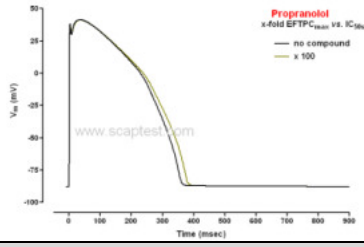
AFKr, AFNaL and AFCaL = active fraction (%) of the I_{Kr}, I_{NaL} and I_{CaL}

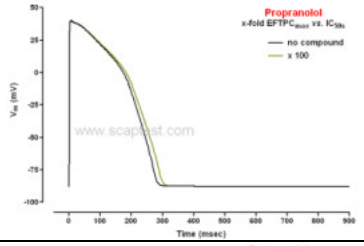
Human epicardial myocytes



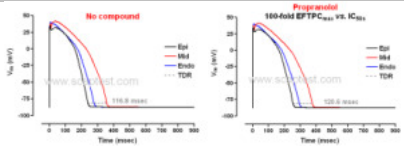
Human midmyocardial myocytes



Human endocardial myocytes

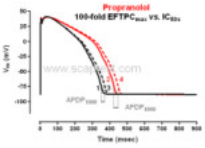


Transmural dispersion of repolarisation

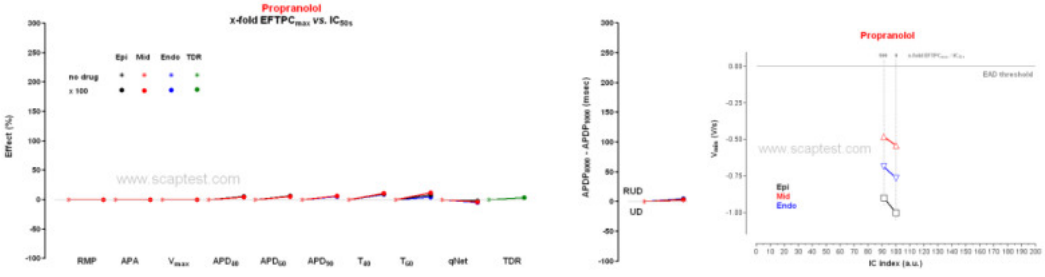


Reverse use dependence on midmyocardial myocytes

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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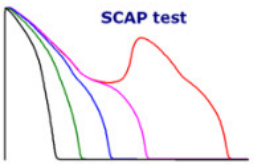

Drug

Quetiapine

Dopamine D_2 and serotonin 5-HT_2 receptor antagonist used to treat major depressive and bipolar disorders or schizophrenia

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 10.471 µM (1.0)
I_{Kr} : 3.802 µM (1.0)
I_{Na} : ---- µM (---)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ [1]

0.4619 µM

TdP risk

Redfern [2] : no published report of TdP (class 5)
Kramer [3] : not reported
CredibleMeds [4] : conditional risk of TdP (class 3)
CiPA [5] : not reported
WP [6] : 3/3 (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_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 = $APD_{90}P_{4000}$-$APD_{90}P_{1000}$
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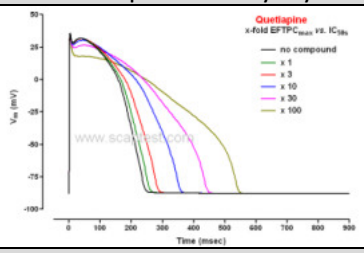
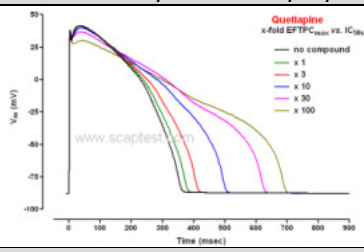
IC index = (AFKr/((AFNaL+AFCaL)/2))*100
where
AFKr, AFNaL and AFCaL = active fraction (%) of the I_{Kr}, I_{NaL} and I_{CaL}

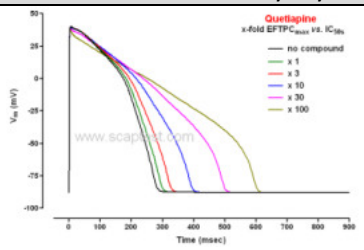
Human epicardial myocytes



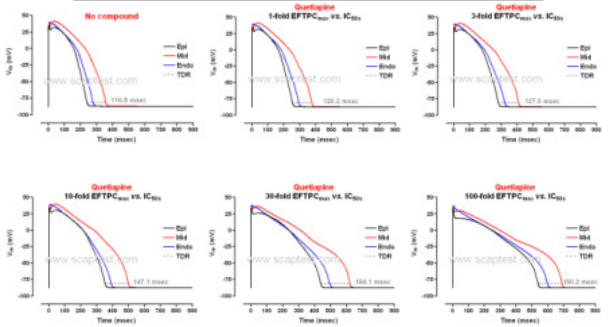
Human midmyocardial myocytes



Human endocardial myocytes

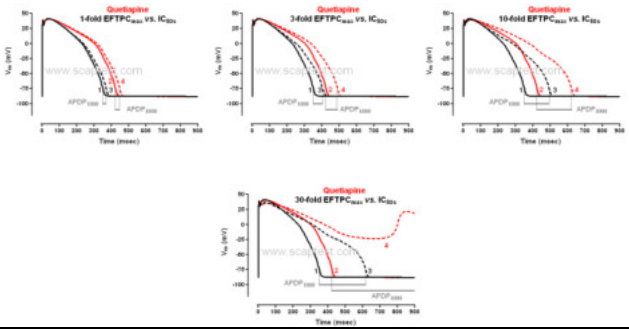


Transmural dispersion of repolarisation

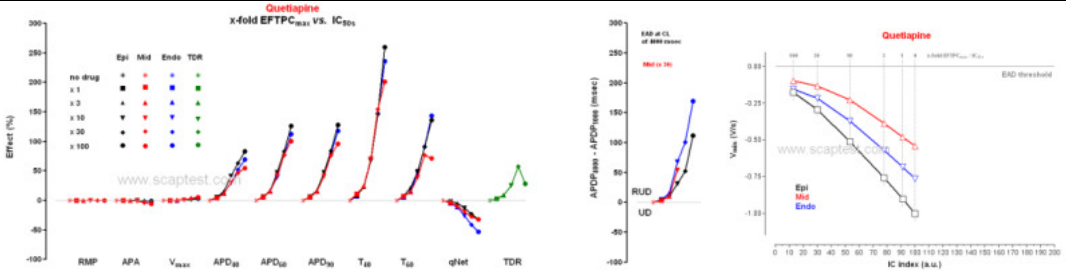


Reverse use dependence on midmyocardial myocytes

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. Wiśniowska B et al. (2017) *Drug discovery today* **22**: 10-16
7. O'Hara T et al. (2011) *PLoS Comput. Biol.* **7**: e1002061_8
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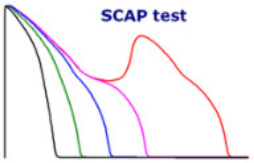
Abbreviations

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

Quinidine

Non selective cardiac ionic channel blocker used as Class IC antiarrhythmic to treat atrial fibrillation or flutter, ventricular arrhythmia or resore normal sinus rhythm

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 6.4 µM (0.68)
I_{to} : ---- µM (---)
I_{Kr} : 0.72 µM (1.06)
I_{NaL} : ---- µM (---)
I_{Na} : 14.6 µM (1.22)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ [1]

3.237 µM

TdP risk

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

Results

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

Simulation conditions:

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

Effect of drugs on AP [8]:

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

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

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:

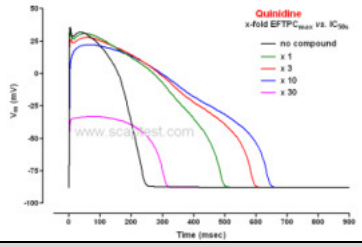
- TDR = APD_{90} mid - APD_{90} epi (at CL of 1000 msec)
- RUD = $APD_{90}P_{4000}$-$APD_{90}P_{1000}$

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

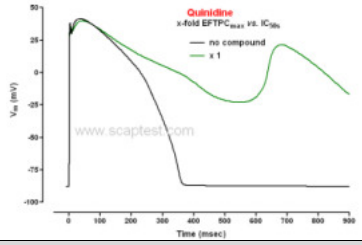
IC index calculation [9]:

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

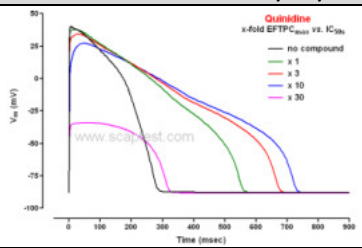
Human epicardial myocytes



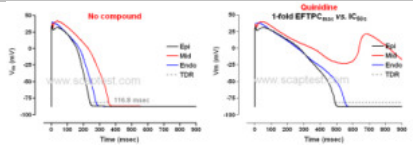
Human midmyocardial myocytes



Human endocardial myocytes

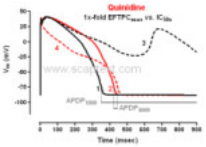


Transmural dispersion of repolarisation

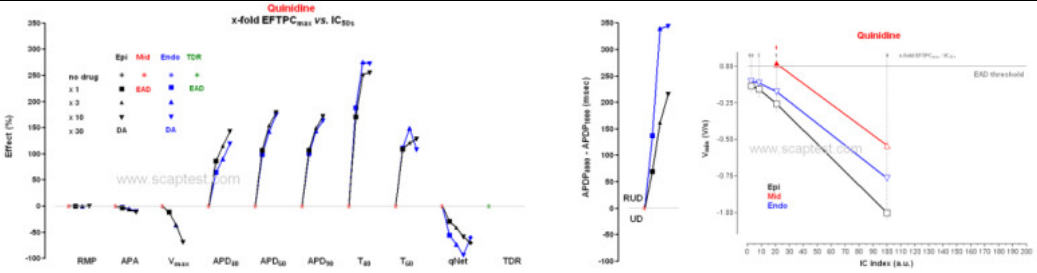


Reverse use dependence on midmyocardial myocytes

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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Abbreviations

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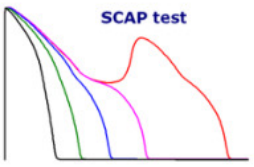

Drug

Quinine

Gametocytocidal activity against malaria parasite used to treat malaria

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 27.178 µM (1.0)
I_{to} : 79.254 µM (1.0)
I_{Kr} : 5.17 µM (1.0)
I_{NaL} : 11.053 µM (0.4)
I_{Na} : 24.151 µM (1.1)
I_{K1} : ---- µM (---)
I_{Ks}: 37.453 µM (1.1)

$EFTPC_{max}$ [1]

3.9567 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] : 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 = 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'

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

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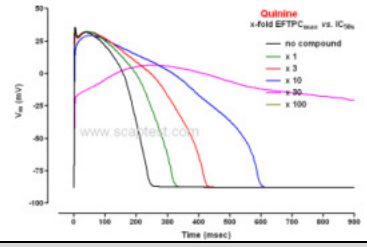
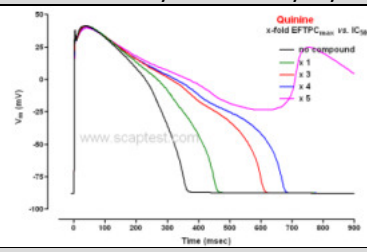
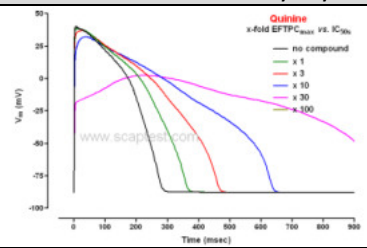
Human epicardial myocytes



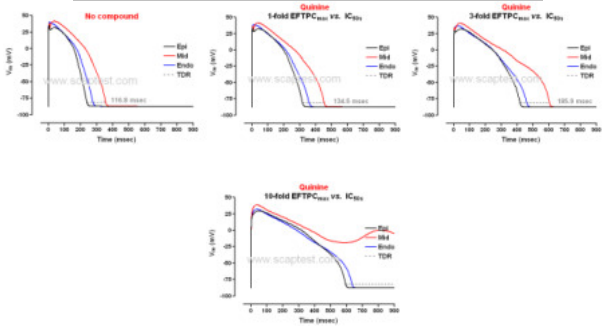
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarisation



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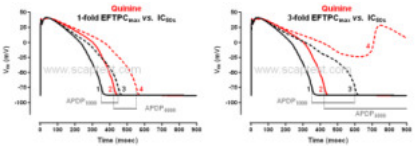
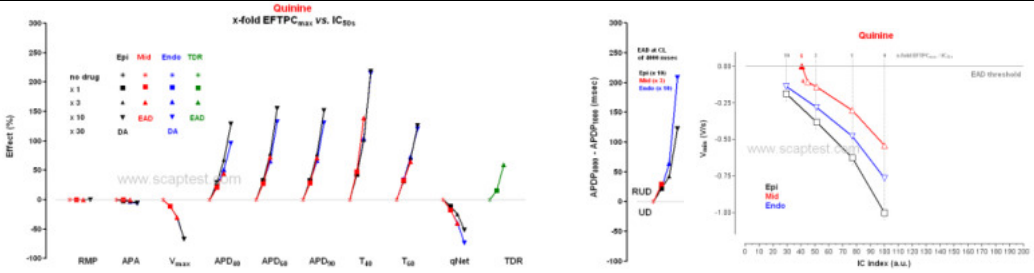


Summary



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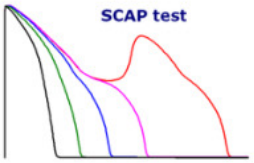

Drug

Raltegravir

HIV integrase inhibitor used to treat HIV infections

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 246.7 µM (1.0)
I_{to} : ---- µM (---)
I_{Kr} : 782.8 µM (1.0)
I_{NaL} : ---- µM (---)
I_{Na} : 824.2 µM (1.0)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ [1]

0.7 µM

TdP risk

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

Results

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

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- External ionic concentrations (mM):
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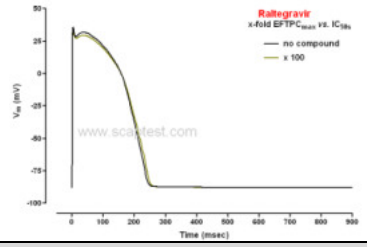
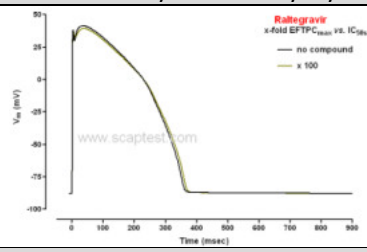
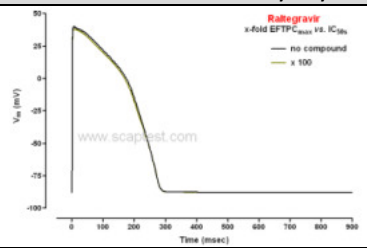
Human epicardial myocytes



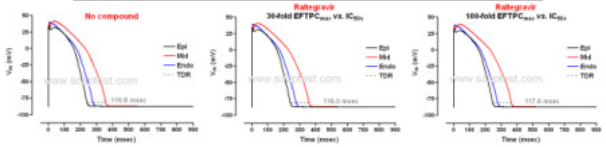
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarisation



Reverse use dependence on midmyocardial myocytes

1 - CL 1000 msec without compound
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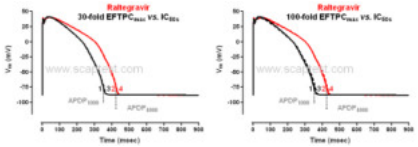
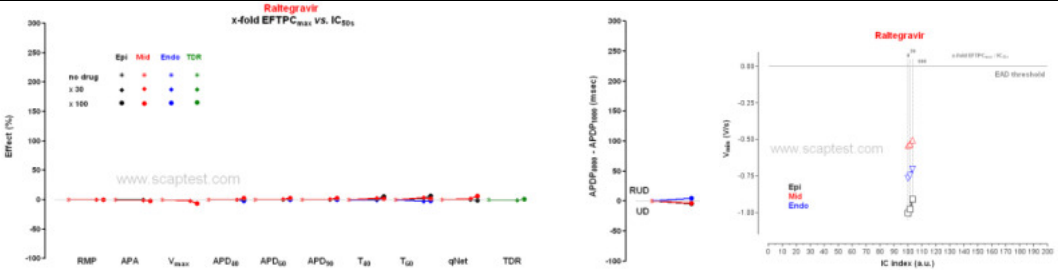


Summary



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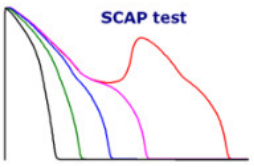
9. Christophe B & Crumb WJ Jr (2019) *J Pharmacol Toxicol Methods* **96** : 15-26

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_{to}+I_{Na}+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

Ranolazine

Voltage-gated K^+ and Na^+ channels blocker used to treat chronic angina

Raw data

IC_{50s} (slope) (1)

I_{CaL} : ---- µM (---)
I_{to} : ---- µM (---)
I_{Kr} : 6.49 µM (0.8)
I_{NaL} : 7.884 µM (0.9)
I_{Na} : ---- µM (---)
I_{K1} : ---- µM (---)
I_{Ks}: ---- µM (---)

$EFTPC_{max}$ (1)

1.9482 µM

TdP risk

Redfern (2) : not reported
Kramer (3) : not reported
CredibleMeds (4) : conditional risk of TdP (class 3)
CiPA (5) : low or no risk of TdP (class 3)
WP (6) : 2/5 (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}

$$I_j = g\,O\,(V - E_{ion})$$

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

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

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

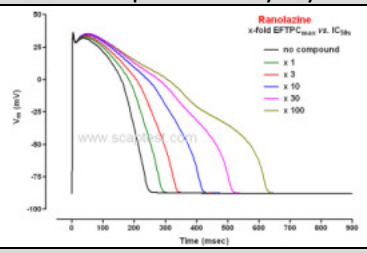
TDR and RUD estimation:

- 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

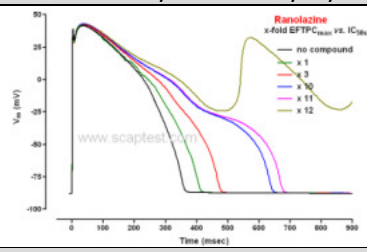
IC index calculation (9):

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

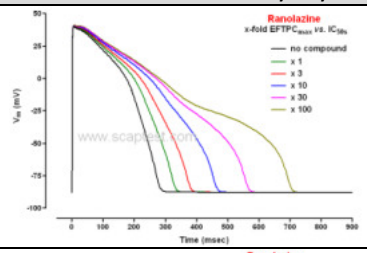
Human epicardial myocytes



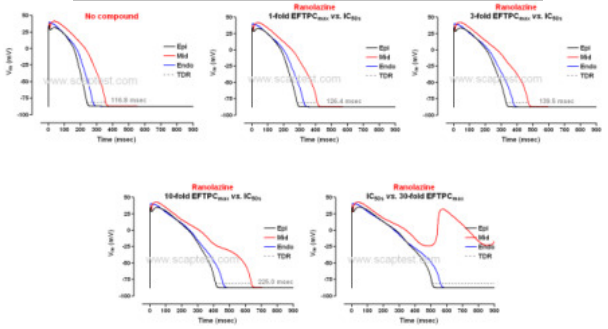
Human midmyocardial myocytes



Human endocardial myocytes

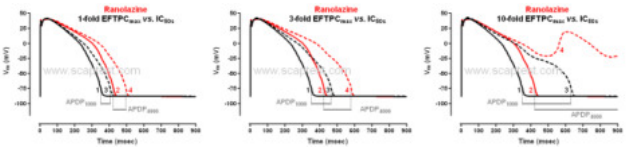


Transmural dispersion of repolarisation

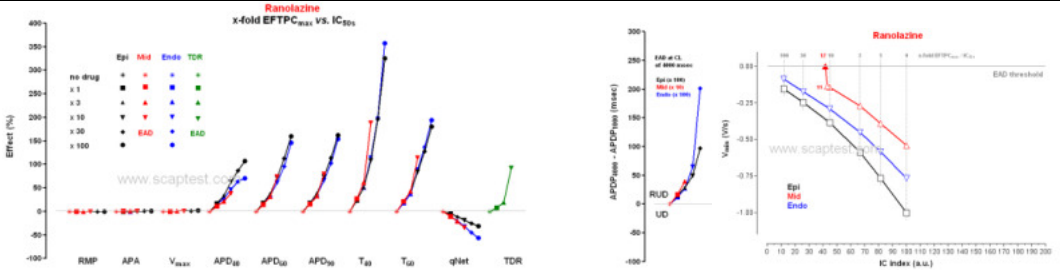


Reverse use dependence on midmyocardial myocytes

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
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6. Wiśniowska B et al. (2017) *Drug discovery today* **22** : 10-16
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Abbreviations

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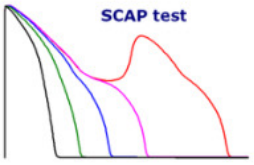

Drug

Ribavirin

Viral RNA and protein synthesis inhibitor used to treat Hepatitis C

Raw data

IC_{50s} (slope) (1)

I_{CaL} : 622.5 µM (1.0)
I_{to} : ---- µM (---)
I_{Kr} : 967.0 µM (1.0)
I_{NaL} : ---- µM (---)
I_{Na} : 2997.5 µM (1.0)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ (1)

27.88 µM

TdP risk

Redfern (2) : not reported
Kramer (3) : non-torsadogenic (class 1)
CredibleMeds (4) : not classified with TdP risk (class 4)
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

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

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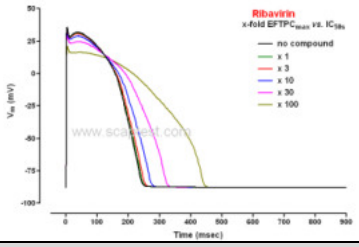
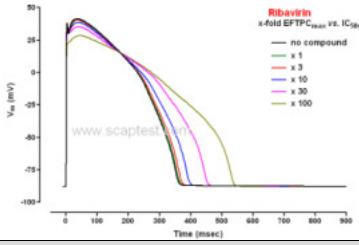
IC index = (AFKr/((AFNaL+AFCaL)/2))*100
where
AFKr, AFNaL and AFCaL = active fraction (%) of the I_{Kr}, I_{NaL} and I_{CaL}

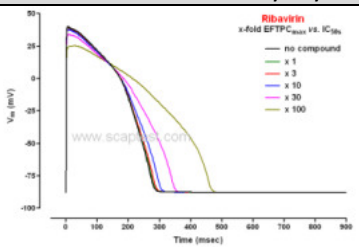
Human epicardial myocytes



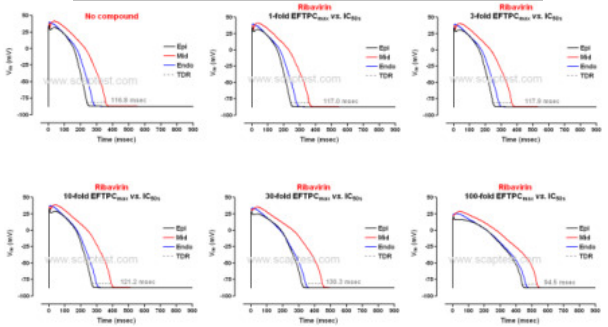
Human midmyocardial myocytes



Human endocardial myocytes

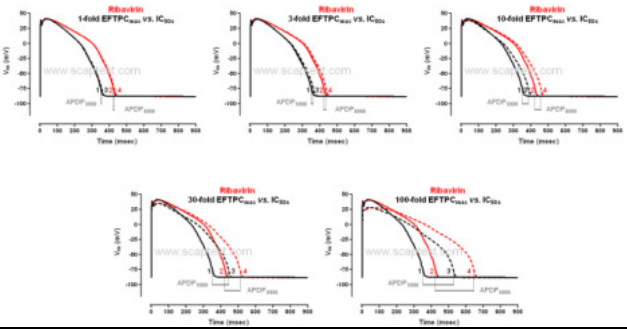


Transmural dispersion of repolarisation

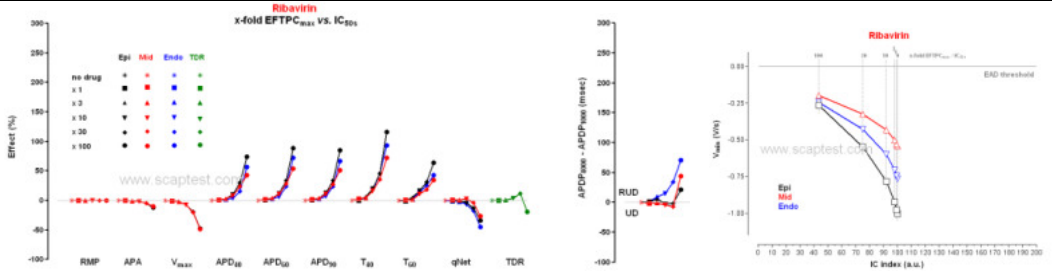


Reverse use dependence on midmyocardial myocytes

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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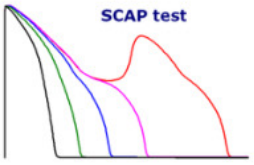

Drug

Risperidone

Dopamine D_2 and serotonin 5-HT_{2A} receptor antagonist used to treat schizophrenia, bipolar mania, psychosis or depression

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 34.2 µM (0.79)
I_{Kr} : 0.26 µM (0.99)
I_{Na} : 43.4 µM (0.98)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ [1]

0.002 µM

TdP risk

Redfern [2] : no published report of TdP (class 5)
Kramer [3] : torsadogenic (class 2)
CredibleMeds [4] : conditional risk of TdP (class 3)
CiPA [5] : intermediate risk of TdP (class 2)
WP [6] : 5/5 (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)
- RUD = $APD_{90}P_{4000}$-$APD_{90}P_{1000}$

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
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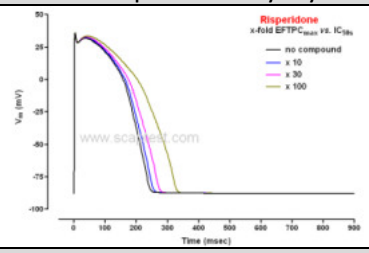
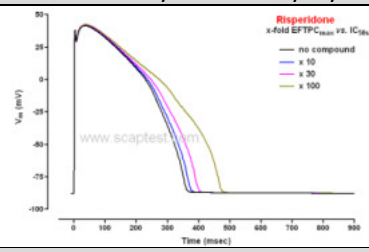
AFKr, AFNaL and AFCaL = active fraction (%) of the I_{Kr}, I_{NaL} and I_{CaL}

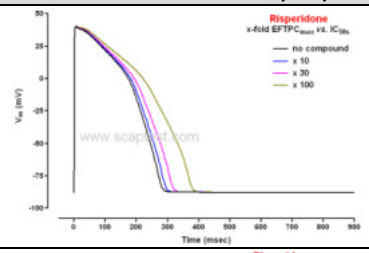
Human epicardial myocytes



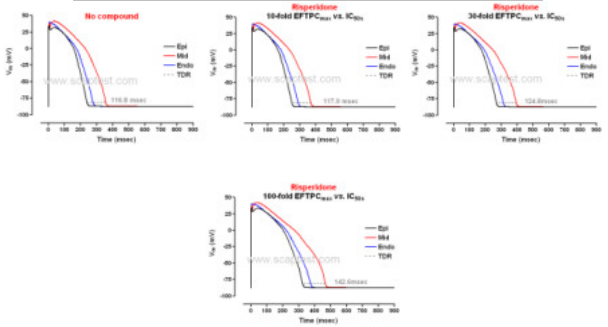
Human midmyocardial myocytes



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
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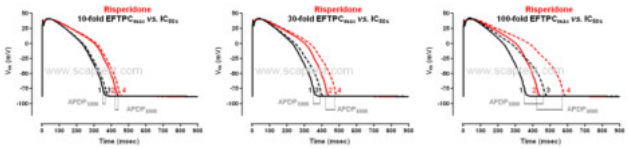
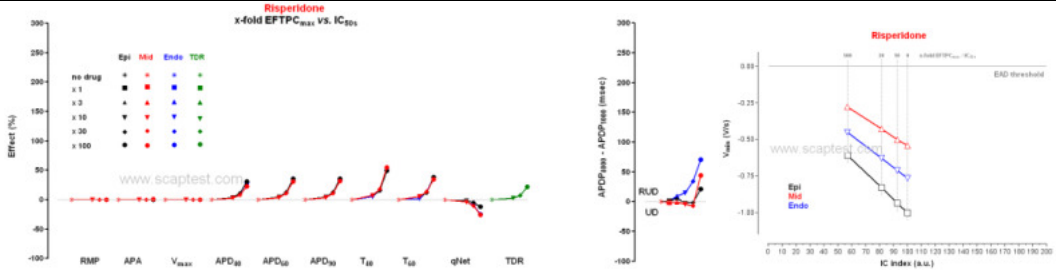


Summary



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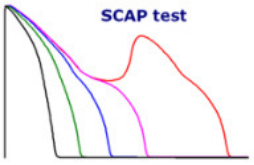

Drug

Ritonavir

HIV protease inhibitor used to treat HIV infections

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 8.228 µM (1.3)
I_{Kr} : 5.157 µM (1.0)
I_{Na} : ---- µM (---)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : 7.175 µM (0.7)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ [1]

0.4369 µM

TdP risk

Redfern [2] : not reported
Kramer [3] : not reported
CredibleMeds [4] : not reported
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):
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$I_j = g_j O (V - E_{ion})$ 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'

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

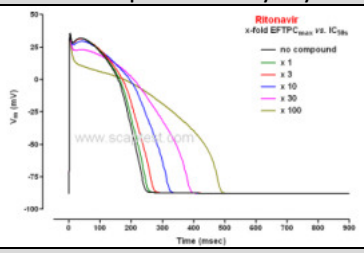
TDR and RUD estimation:

- 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

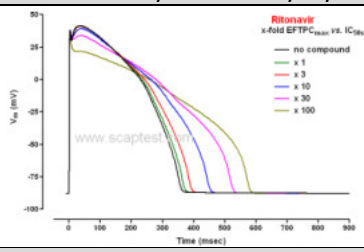
IC index calculation [9]:

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

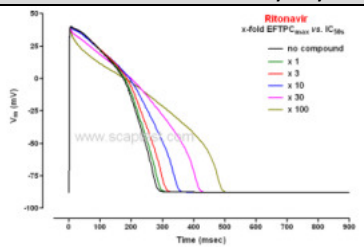
Human epicardial myocytes



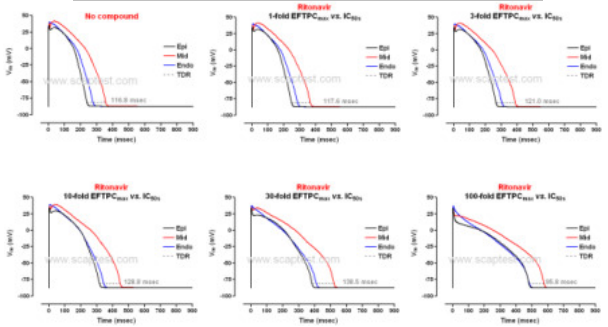
Human midmyocardial myocytes



Human endocardial myocytes

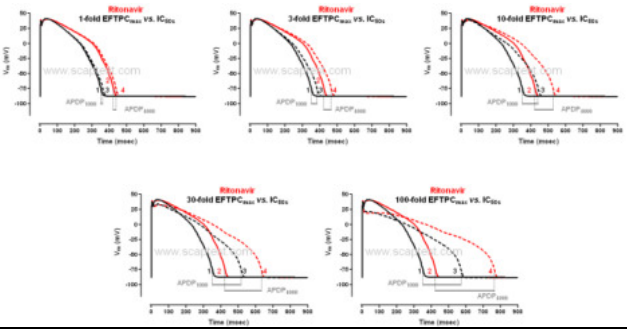


Transmural dispersion of repolarisation

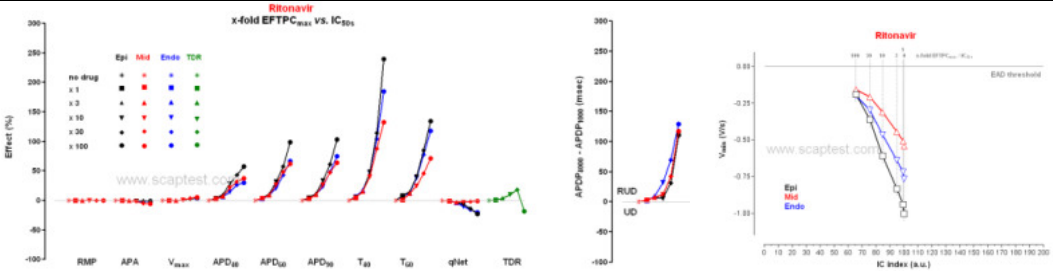


Reverse use dependence on midmyocardial myocytes

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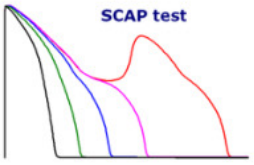
8. Mirams GR et al. (2011) *Cardiovasc. Res.* **91** : 53-61
9. Christophe B & Crumb WJ Jr (2019) *J Pharmacol Toxicol Methods* **96** : 15-26

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_{90}-APD_{40} or APD_{50} (°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

Rufinamide

Voltage-gated Na^+ and Ca^{++} channel blocker used to treat seizures in childhood epilepsy

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 264.448 µM (0.9)
I_{to} : ---- µM (---)
I_{Kr} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{Na} : ---- µM (---)
I_{K1} : ---- µM (---)
I_{Ks}: ---- µM (---)

$EFTPC_{max}$ [1]

83.1269 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
- 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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- RUD = $APD_{90}P_{4000}$-$APD_{90}P_{1000}$
  where
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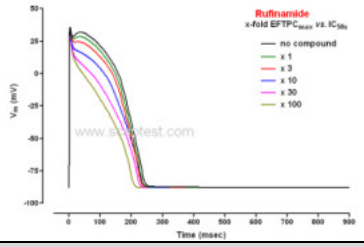
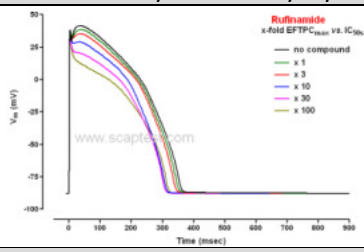
IC index calculation [9]:

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

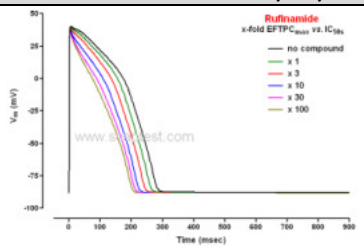
Human epicardial myocytes



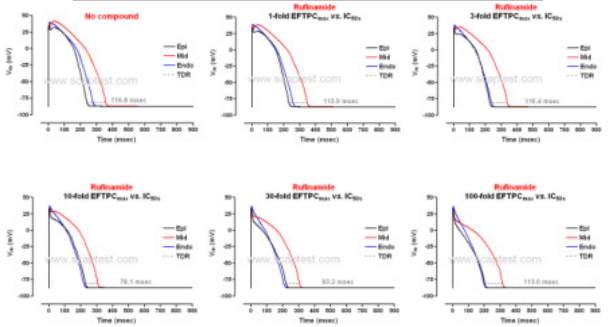
Human midmyocardial myocytes



Human endocardial myocytes

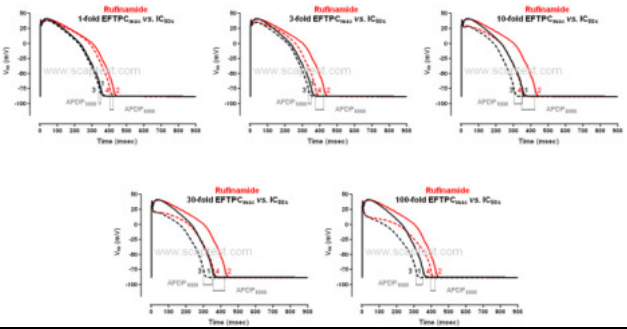


Transmural dispersion of repolarisation

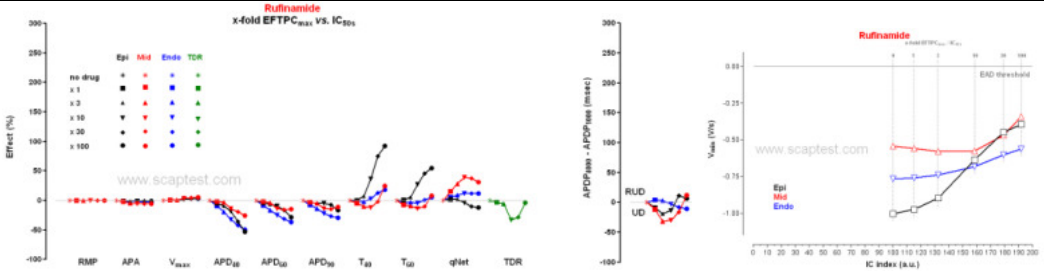


Reverse use dependence on midmyocardial myocytes

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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Abbreviations

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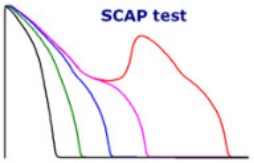

Drug

Saquinavir

HIV protease inhibitor used to treat HIV infections

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 1.9 µM (1.15)
I_{Kr} : 16.9 µM (1.72)
I_{Na} : 12.1 µM (2.34)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ [1]

0.13 µM

TdP risk

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

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

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D= drug concentration (EFTPC for example)
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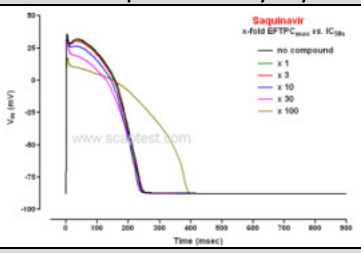
TDR and RUD estimation:
- TDR = APD_{90} mid - APD_{90} epi (at CL of 1000 msec)
- RUD = $APD_{90}P_{x400}$- $APD_{90}P_{1000}$

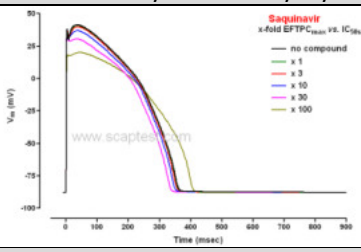
where
$APD_{90}P_x$ = APD_{90} with - APD_{90} without compound at CL x

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}.

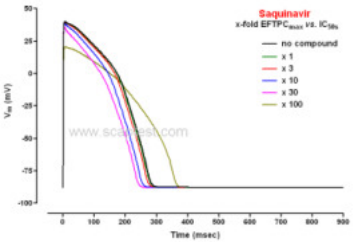
Human epicardial myocytes



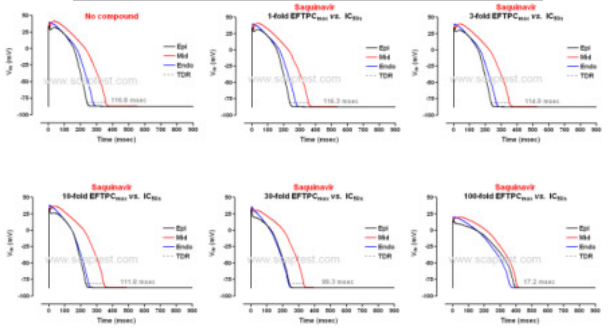
Human midmyocardial myocytes



Human endocardial myocytes

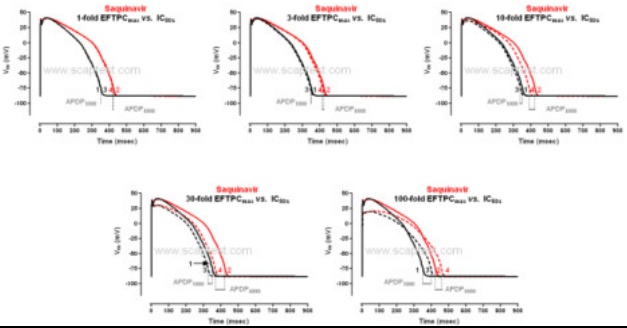


Transmural dispersion of repolarisation

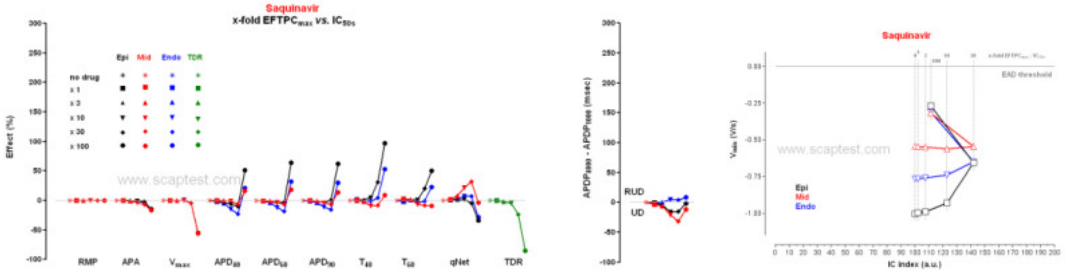


Reverse use dependence on midmyocardial myocytes

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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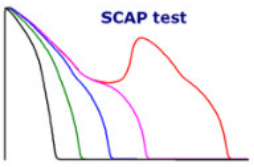

Drug

Sertindole

Dopamine D_2, serotonin 5-HT_{2A} and 5-HT_{2C} and σ_1-adrenergic receptors antagonist used to treat schizophrenia
no longer marketed in UK, Bulgaria and Spain (Onakpoya et al (2016) *BMC Med.* **14**: 10)

Raw data

IC_{50s} (slope) (1)

I_{CaL} : 6.3 µM (1.29)
I_{Kr} : 0.033 µM (1.25)
I_{Na} : 6.9 µM (1.19)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ (1)

0.002 µM

TdP risk

Redfern (2) : unacceptable risk of TdP (class 2)
Kramer (3) : torsadogenic (class 2)
CredibleMeds (4) : known risk of TdP (class 1)
CiPA (5) : not reported
WP (6) : 11/1 (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
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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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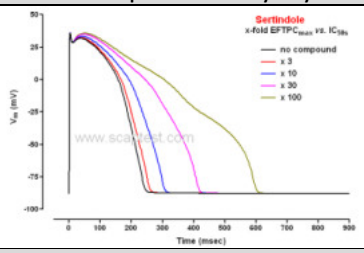
$g_j = g_{control,j}\left[1 + \left(\frac{D}{IC50_j}\right)^n\right]^{-1}$ (g = maximal conductance of channel 'j', $g_{control,j}$ = drug-free maximal conductance of channel 'j', IC50 = 50% of inhibition of a drug for channel 'j', D= drug concentration (EFTPC for example), n= hill slope)

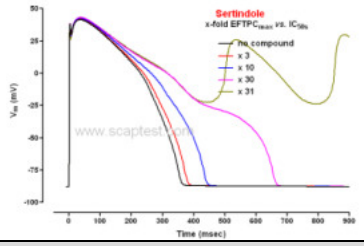
TDR and RUD estimation:
- TDR = APD_{95} mid - APD_{95} epi (at CL of 1000 msec)
- RUD = $APD_{90}P_{x1000}$-$APD_{90}P_{1000}$ where $APD_{90}P_x$ = APD_{90} with - APD_{90} without compound at CL x

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}

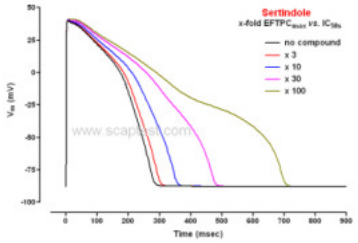
Human epicardial myocytes



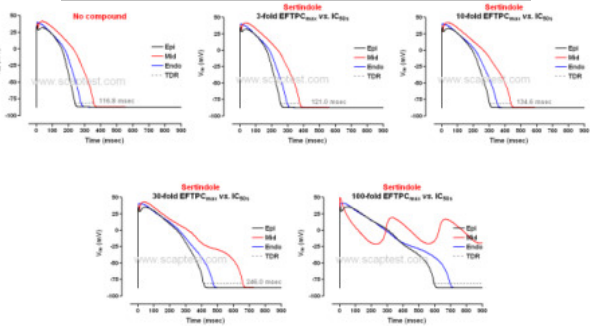
Human midmyocardial myocytes



Human endocardial myocytes

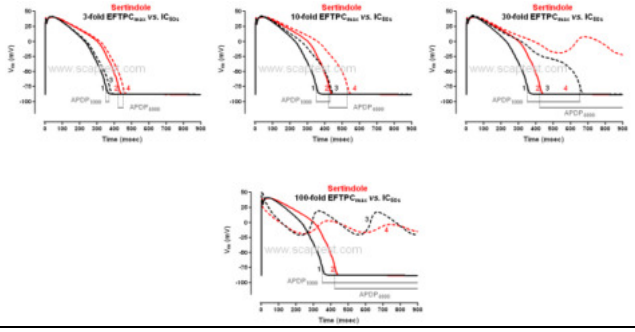


Transmural dispersion of repolarisation

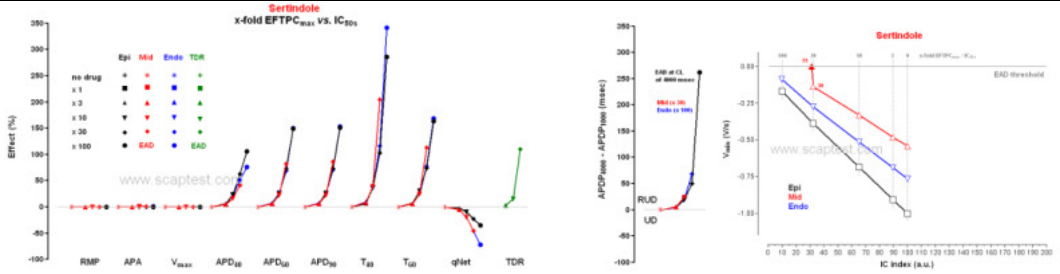


Reverse use dependence on midmyocardial myocytes

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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4. Woosley RL (2015) www.CredibleMeds.org
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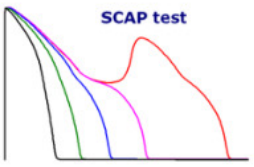
Abbreviations

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_{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

Sertraline

Serotonin reuptake inhibitor used to treat major depressive or social anxiety disorders

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 2.6 µM (1.9)
I_{to} : ---- µM (---)
I_{Kr} : 0.7 µM (1.3)
I_{NaL} : ---- µM (---)
I_{Na} : 6.1 µM (0.7)
I_{K1} : 10.5 µM (2.1)
I_{Ks} : 12.3 µM (2.5)

$EFTPC_{max}$ [1]

0.6 µM

TdP risk

Redfern [2] : not reported
Kramer [3] : not reported
CredibleMeds [4] : conditionnal risk of TdP (class 3)
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:

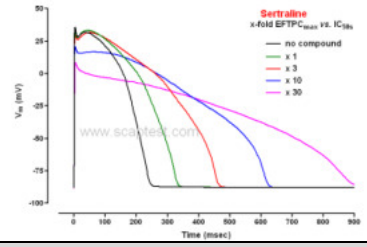
- TDR = APD_{90} mid - APD_{90} epi (at CL of 1000 msec)
- RUD = $APD_{90}P_{4000}$-$APD_{90}P_{1000}$

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

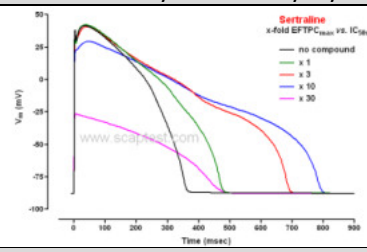
IC index calculation [9]:

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

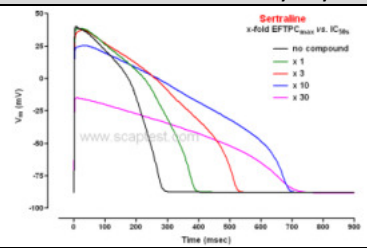
Human epicardial myocytes



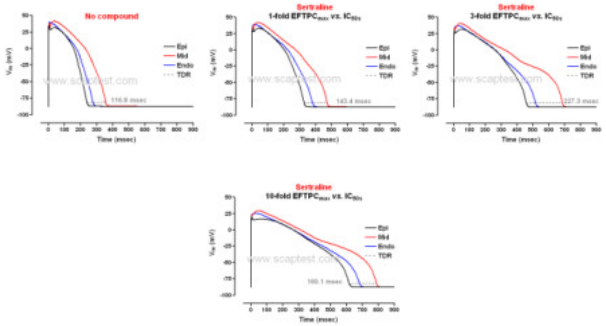
Human midmyocardial myocytes



Human endocardial myocytes

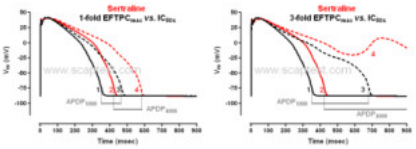


Transmural dispersion of repolarisation

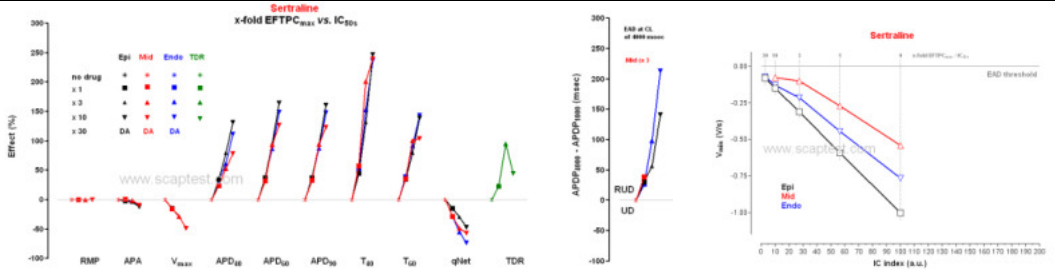


Reverse use dependence on midmyocardial myocytes

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

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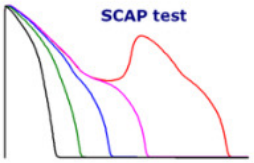

Drug

Sildenafil

Phosphodiesterase PDE-5 inhibitor used to treat erectile dysfunction

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 100.0 µM (1.0)
I_{to} : 501.187 µM (1.0)
I_{Kr} : 31.623 µM (1.0)
I_{NaL} : ---- µM (---)
I_{Na} : 501.187 µM (1.0)
I_{K1} : ---- µM (---)
I_{Ks} : 398.107 µM (1.0)

$EFTPC_{max}$ [1]

0.071513 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'
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IC index = (AFKr/((AFNaL+AFCaL)/2))*100
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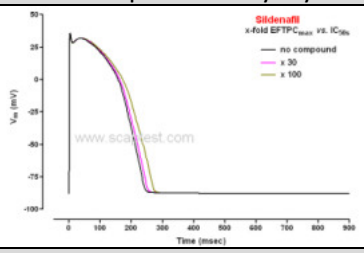
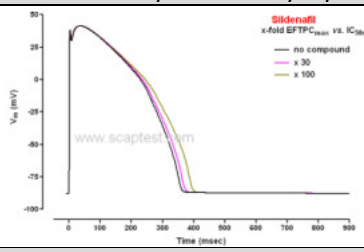
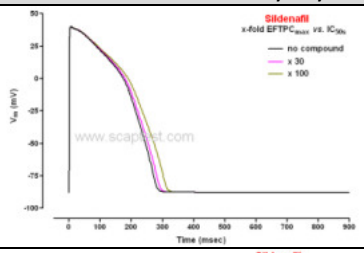
Human epicardial myocytes



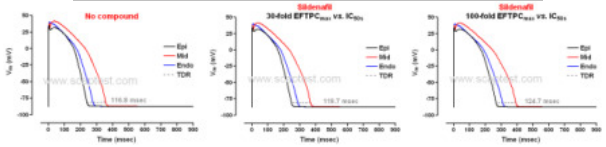
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarisation



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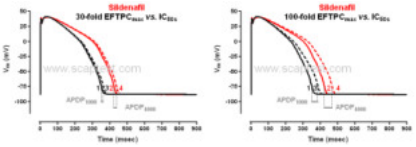
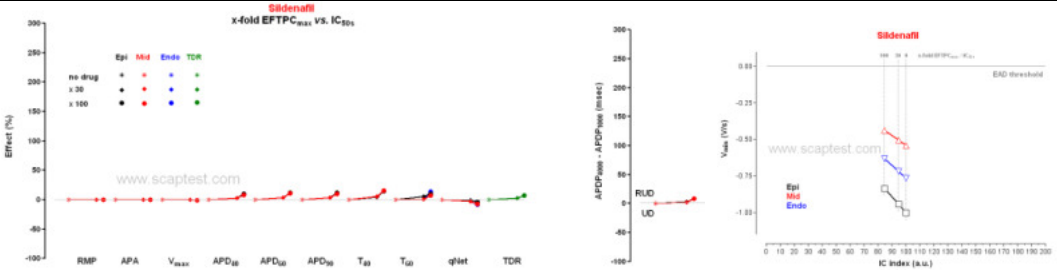


Summary



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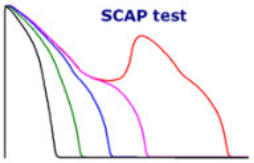

Drug

Silodosin

σ_{1A}-adrenoceptor antagonist used to treat begnin prostatic hyperplasia

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 794.3 µM (1.0)
I_{to} : 316.228 µM (1.0)
I_{Kr} : 7.943 µM (1.0)
I_{NaL} : ---- µM (---)
I_{Na} : 63.096 µM (1.0)
I_{K1} : ---- µM (---)
I_{Ks} : 251.189 µM (1.0)

$EFTPC_{max}$ [1]

0.009409 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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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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IC50 = 50% of inhibition of a drug for channel 'j'
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IC index = (AFKr/((AFNaL+AFCaL)/2))*100
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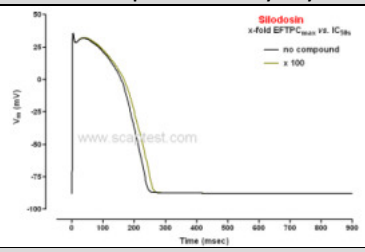
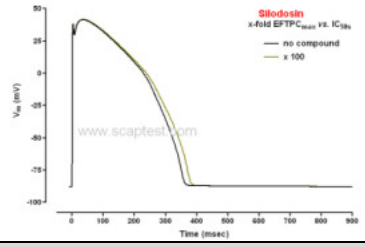
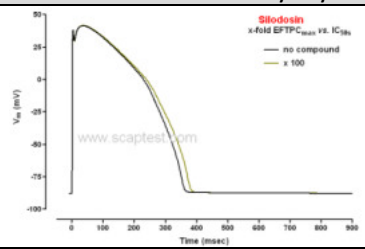
Human epicardial myocytes



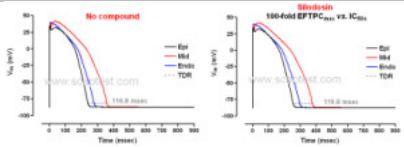
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of 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
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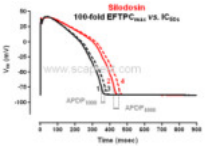
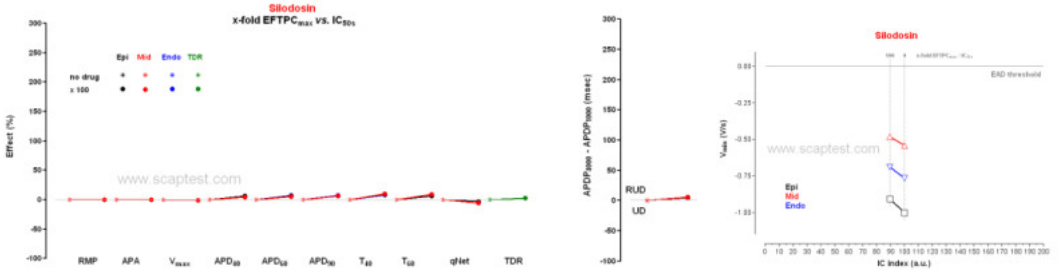


Summary



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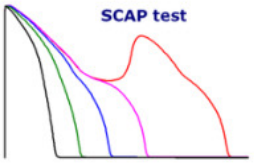

Drug

Sitagliptin

Dipeptidyl peptidase-4 inhibitor used to treat type 2 diabetes mellitus

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 147.1 µM (1.0)
I_{Kr} : 174.7 µM (1.0)
I_{Na} : 1220.8 µM (1.0)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ [1]

0.442 µM

TdP risk

Redfern [2] : not reported
Kramer [3] : non-torsadogenic (class 1)
CredibleMeds [4] : not reported
CiPA [5] : not reported
WP [6] : 0/2(TdP+/TdP-)

Results

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- 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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- 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'

$$g_j = g_{control,j}\left[1 + \left(\frac{D}{nC50_j}\right)^n\right]^{-1}$$

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:

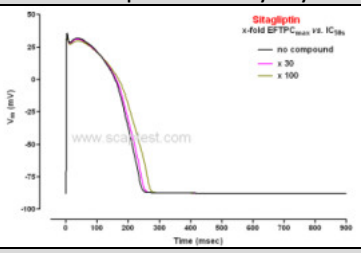
- TDR = APD_{90} mid - APD_{90} epi (at CL of 1000 msec)
- RUD = $APD_{90}P_{4000}$-$APD_{90}P_{1000}$

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

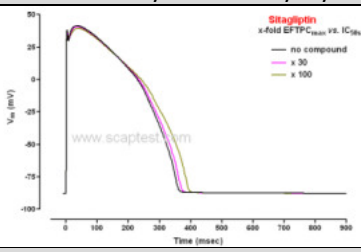
IC index calculation [9]:

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

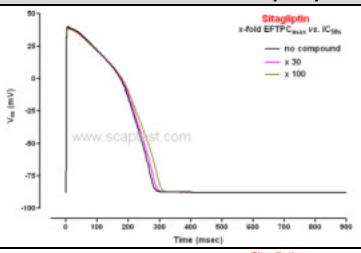
Human epicardial myocytes



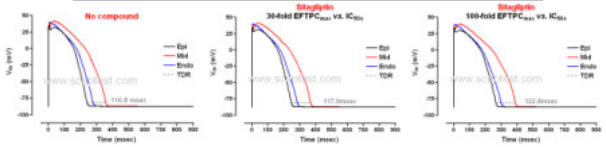
Human midmyocardial myocytes



Human endocardial myocytes

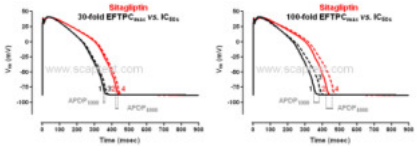


Transmural dispersion of repolarisation

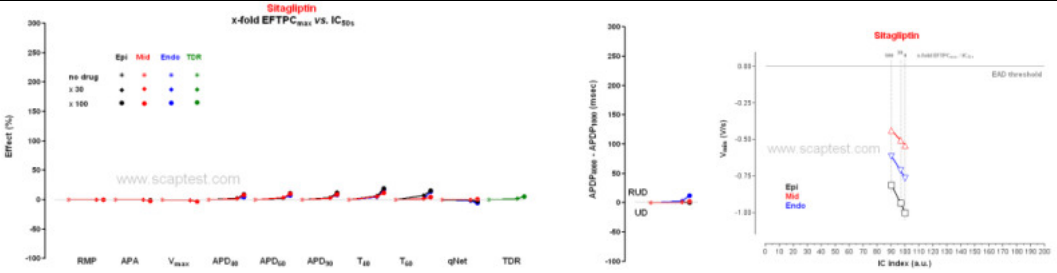


Reverse use dependence on midmyocardial myocytes

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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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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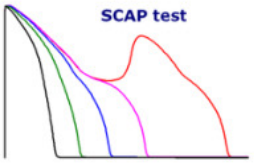

Drug

Solifenacin

Muscarinic M_2 and M_3 receptor antagonist used to treat urinary incontinence

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 4.3 µM (1.47)
I_{to} : ---- µM (---)
I_{Kr} : 0.28 µM (0.90)
I_{NaL} : ---- µM (---)
I_{Na} : 1.5 µM (1.32)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ [1]

0.003 µM

TdP risk

Redfern [2] : not reported
Kramer [3] : torsadogenic (class 2)
CredibleMeds [4] : conditional risk of TdP (class 3)
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
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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 = 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'

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

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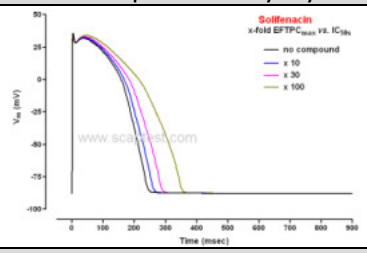
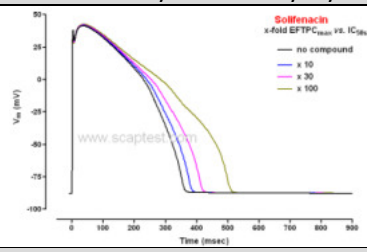
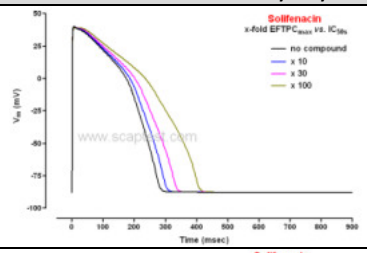
Human epicardial myocytes



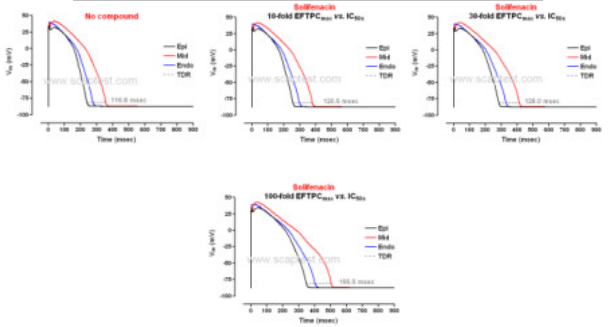
Human midmyocardial myocytes



Human endocardial myocytes

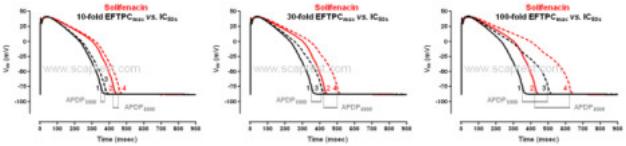


Transmural dispersion of repolarisation

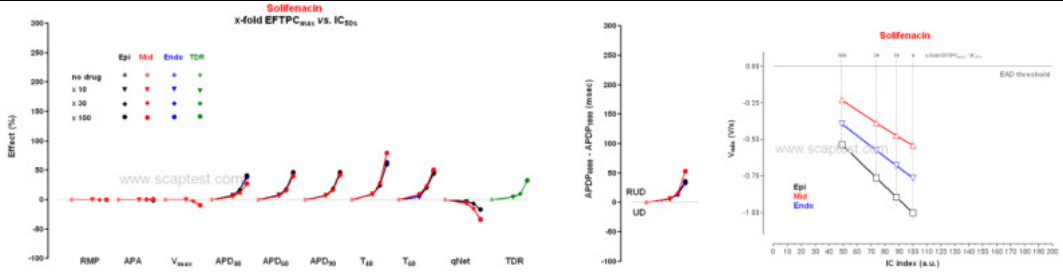


Reverse use dependence on midmyocardial myocytes

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

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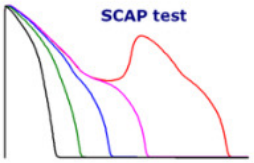

Drug

Sotalol

β1-adrenoceptor antagonist used to treat ventricular arrhythmia or maintain sinus rhythm in atrial fibrillation

Raw data

IC_{50s} (slope) (1)

I_{CaL} : 193.3 µM (1.0)
I_{to} : ---- µM (---)
I_{Kr} : 111.4 µM (0.73)
I_{NaL} : ---- µM (---)
I_{Na} : 7013.9 µM (1.0)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ (1)

14.69 µM

TdP risk

Redfern (2) : class IA or III antiarrhythmics (class 1)
Kramer (3) : torsadogenic (class 2)
CredibleMeds (4) : known risk of TdP (class 1)
CiPA (5) : high risk of TdP (class 1)
WP (6) : 14/0 (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
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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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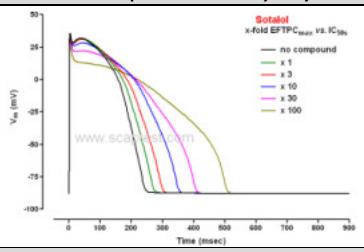
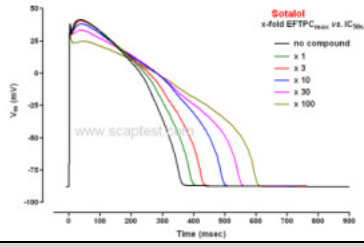
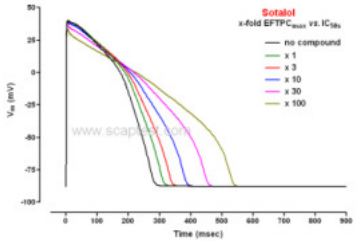
Human epicardial myocytes



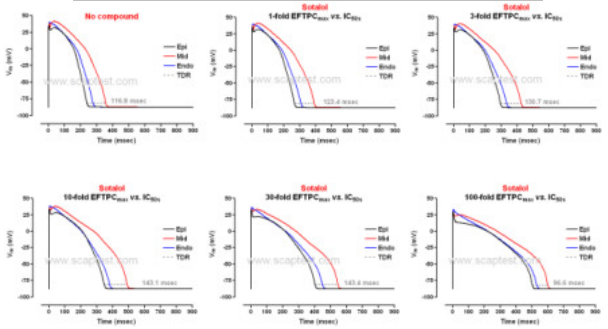
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarisation



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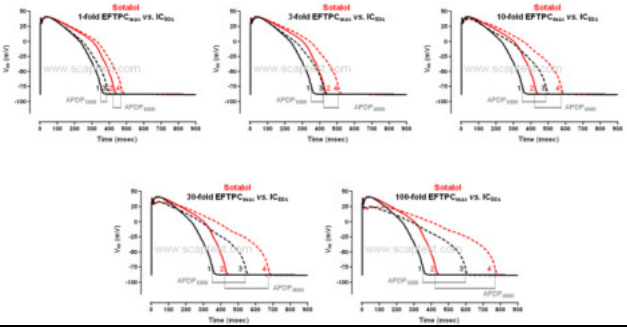

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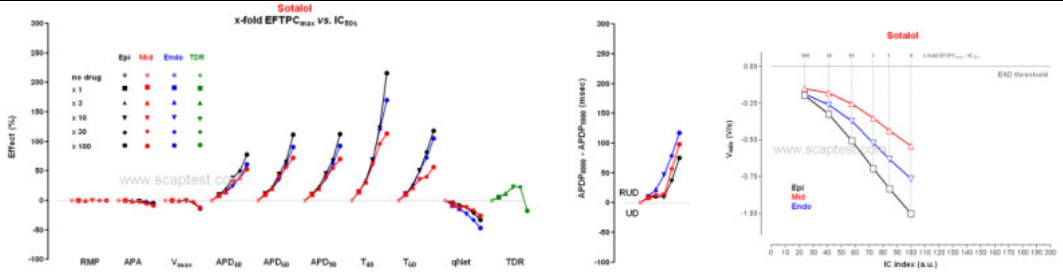

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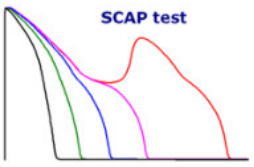

Drug

Sparfloxacin

Fluoroquinolone antibiotic used to treat bacterial respiratory infections and sinusitis
no longer marketed in Europe and USA (Onakpoya et al (2016) *BMC Med.* **14**: 10)

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 88.8 µM (1.0)
I_{Kr} : 22.1 µM (0.93)
I_{Na} : 2555.0 µM (1.0)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ [1]

1.766 µM

TdP risk

Redfern [2] : isolated reports of TdP (class 4)
Kramer [3] : torsadogenic (class 2)
CredibleMeds [4] : known risk of TdP (class 1)
CiPA [5] : not reported
WP [6] : 8/2 (TdP+/TdP-)

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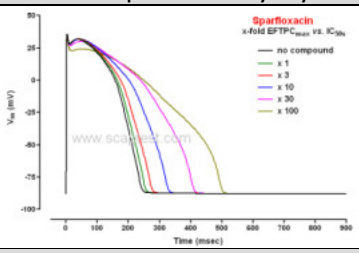
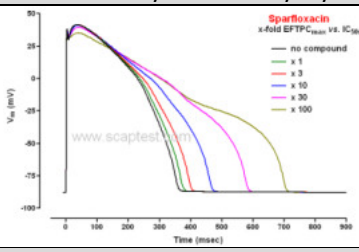
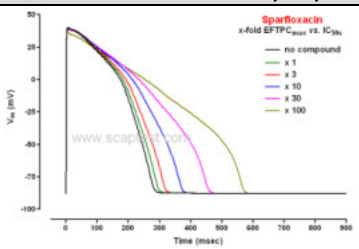
Human epicardial myocytes



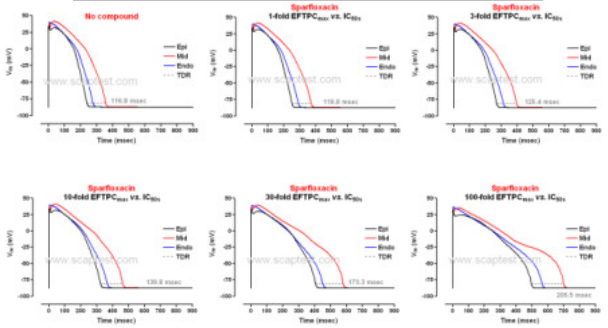
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarisation



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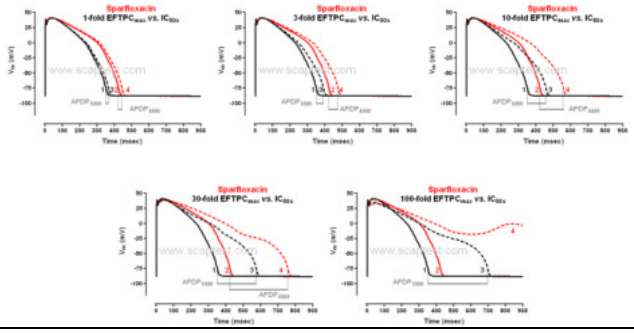
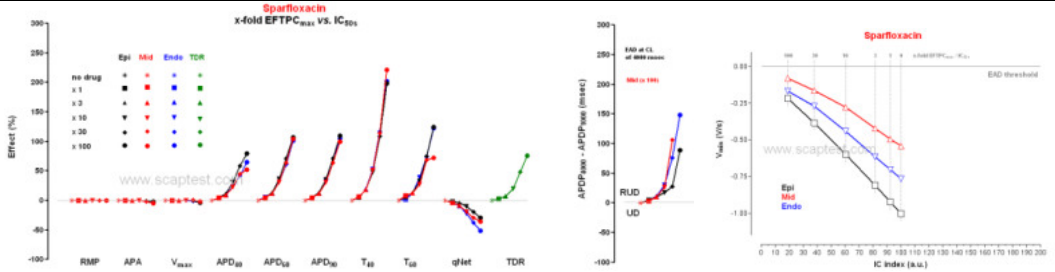
1 - CL 1000 msec without compound
2 - CL 4000 msec without compound
3 - CL 1000 msec with compound
4 - CL 4000 msec with compound



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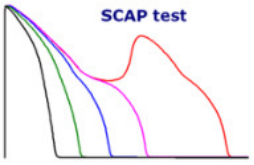
6. Wiśniowska B et al. (2017) *Drug discovery today* **22** : 10-16
7. O'Hara T et al. (2011) *PLoS Comput. Biol.* **7** : e1002061_8
8. Mirams GR et al. (2011) *Cardiovasc. Res.* **91** : 53-61
9. Christophe B & Crumb WJ Jr (2019) *J Pharmacol Toxicol Methods* **96** : 15-26

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_{50} (°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

Sunitinib

Tyrosine kinase inhibitor used to treat renal cell carcinoma and gastrointestinal stromal tumor

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 33.4 µM (1.09)
I_{to} : ---- µM (---)
I_{Kr} : 1.2 µM (1.0)
I_{NaL} : ---- µM (---)
I_{Na} : 16.5 µM (1.22)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ [1]

0.013 µM

TdP risk

Redfern [2] : not reported
Kramer [3] : torsadogenic (class 2)
CredibleMeds [4] : possible risk of TdP (class 2)
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}

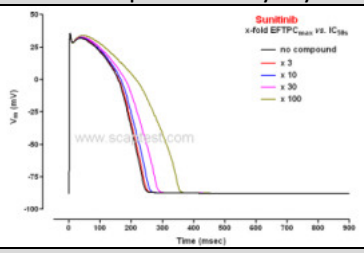
$I_j = g_j O(V - E_{ion})$ (g = maximal conductance of channel j; O=open probability of channel j; V= voltage membrane; E_{ion} = reversal potential for species of ions which flows through channel j)

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

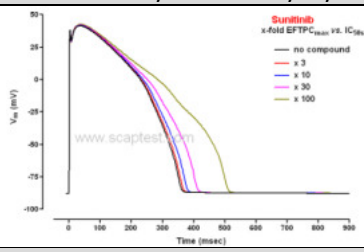
TDR and RUD estimation:
- TDR = APD_{90} mid - APD_{90} epi (at CL of 1000 msec)
- RUD = $APD_{90}P_{4000}$-$APD_{90}P_{1000}$ where $APD_{90}P_x$ = APD_{90} with - APD_{90} without compound at CL x

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}.

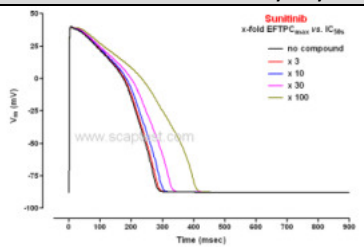
Human epicardial myocytes



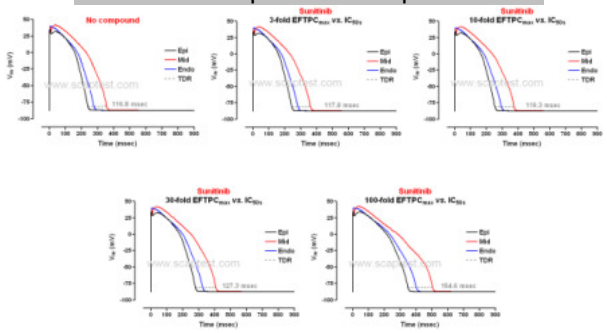
Human midmyocardial myocytes



Human endocardial myocytes

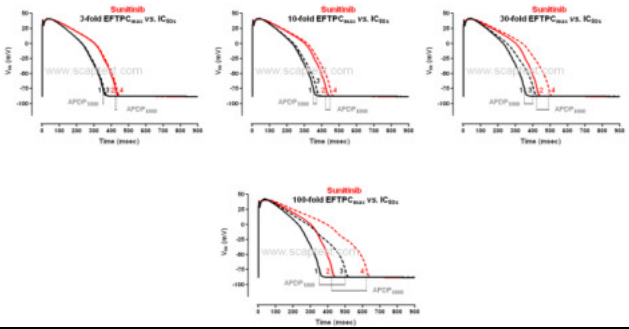


Transmural dispersion of repolarisation

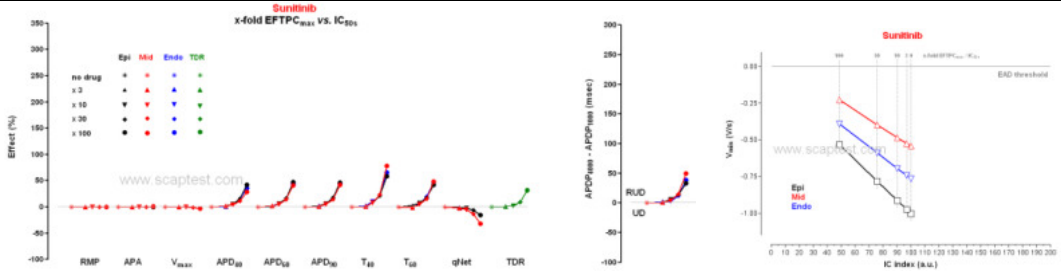


Reverse use dependence on midmyocardial myocytes

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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8. Mirams GR et al. (2011) *Cardiovasc. Res.* **91** : 53-61
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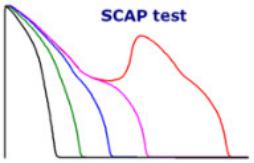
Abbreviations

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_{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

Tadalafil

Phosphodiesterase PDE-5 inhibitor used to treat erectile dysfunction, begnin prostatic hyperplasia and pulmonary arterial hypertension

Raw data

IC_{50s} (slope) (1)

I_{CaL} : ----- µM (---)
I_{Kr} : 100.0 µM (1.0)
I_{Na} : 125.9 µM (1.0)
I_{Ks} : 158.49 µM (1.0)
I_{to} : ----- µM (---)
I_{NaL} : ----- µM (---)
I_{K1} : ----- µM (---)

$EFTPC_{max}$ (1)

0.13605 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'
$g_{control,j}$ = 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:

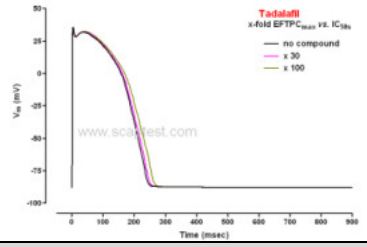
- TDR = APD_{90} mid - APD_{90} epi (at CL of 1000 msec)
- RUD = $APD_{90}P_{4000}$-$APD_{90}P_{1000}$

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

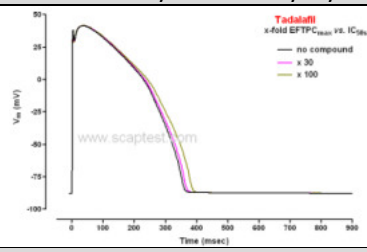
IC index calculation (9):

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

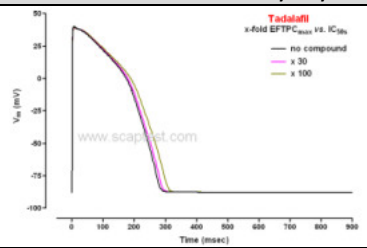
Human epicardial myocytes



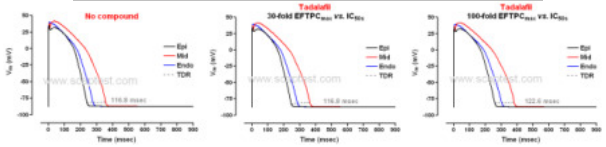
Human midmyocardial myocytes



Human endocardial myocytes

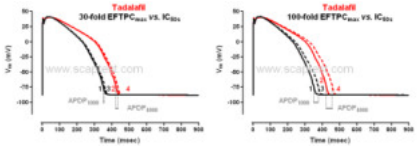


Transmural dispersion of repolarisation

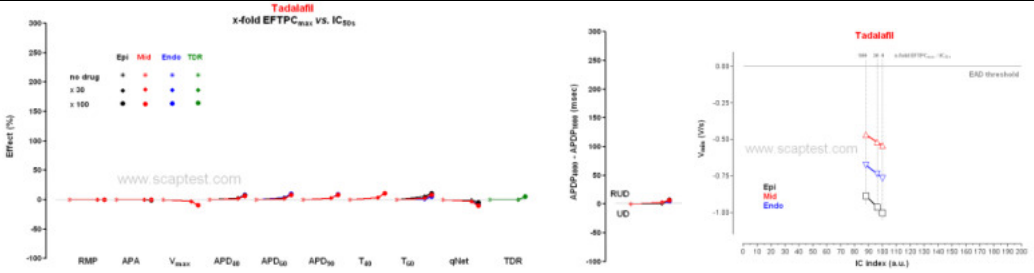


Reverse use dependence on midmyocardial myocytes

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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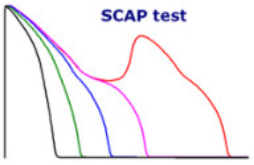


Drug

Tamoxifen

Estrogen receptor modulator used to treat breast cancer

Raw data

IC_{50s} (slope) [1]

I_{CaL} : ---- µM (---)
I_{to} : ---- µM (---)
I_{Kr} : 0.777 µM (1.0)
I_{NaL} : ---- µM (---)
I_{Na} : ---- µM (---)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ [1]

0.018 µM

TdP risk

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

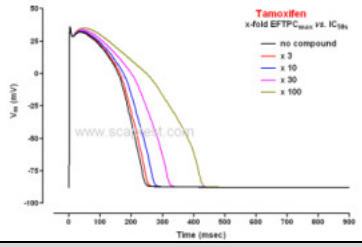
$I_j = g\,O\,(V - E_{ion})$ (g = maximal conductance of channel j; O = open probability of channel j; V = voltage membrane; E_{ion} = reversal potential for species of ions which flows through channel j)

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

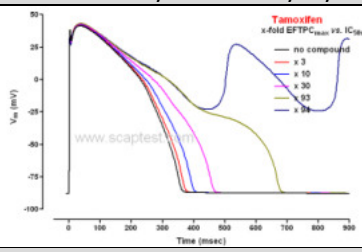
TDR and RUD estimation:
- TDR = APD_{90} mid - APD_{90} epi (at CL of 1000 msec)
- RUD = $APD_{90}P_{4000}$-$APD_{90}P_{1000}$ where $APD_{90}P_x$ = APD_{90} with - APD_{90} without compound at CL x

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}.

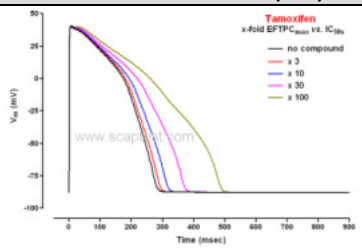
Human epicardial myocytes



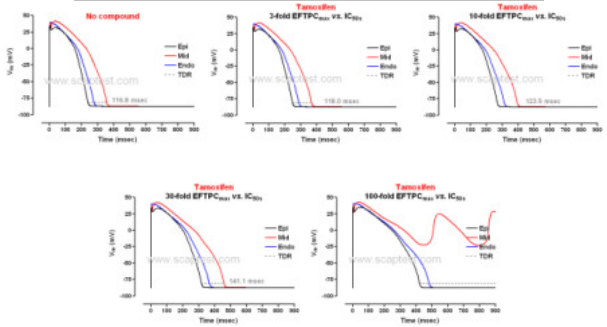
Human midmyocardial myocytes



Human endocardial myocytes

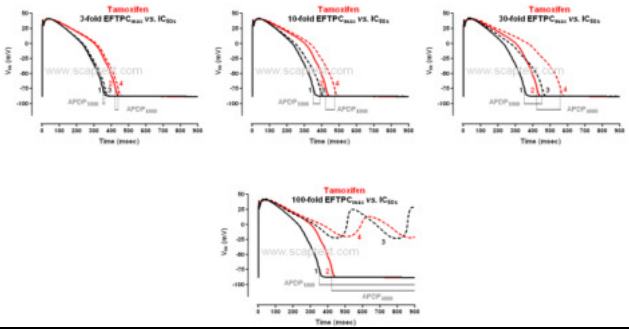


Transmural dispersion of repolarisation

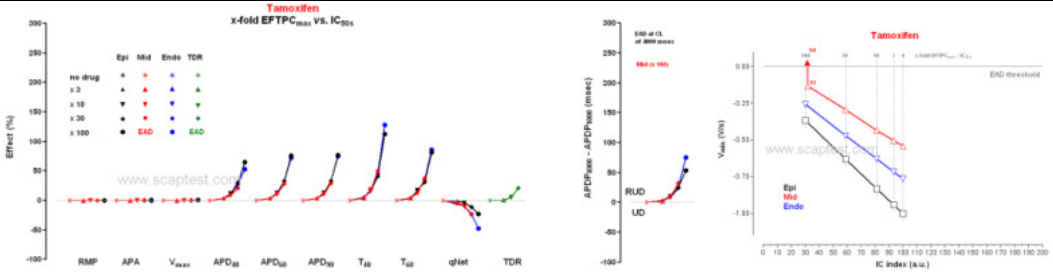


Reverse use dependence on midmyocardial myocytes

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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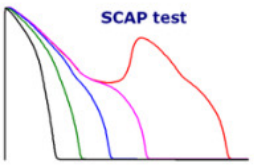

Drug

Tedisamil

Voltage-gated K^+ channel blocker to treat atrial fibrillation

Raw data

IC_{50s} (slope) [1]

I_{CaL} : ---- µM (---)
I_{to} : ---- µM (---)
I_{Kr} : 0.219 µM (1.0)
I_{NaL} : ---- µM (---)
I_{Na} : ---- µM (---)
I_{K1} : ---- µM (---)
I_{Ks} : 6.457 µM (1.0)

$EFTPC_{max}$ [1]

0.085 µM

TdP risk

Redfern [2] : class IA or III antiarrhythmics (class 1)
Kramer [3] : not reported
CredibleMeds [4] : not reported
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):
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$$I_j = g_j O (V - E_{ion})$$

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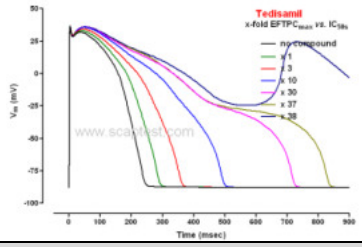
where
$APD_{90}P_x$ = APD_{90} with - APD_{90} without compound at CL x

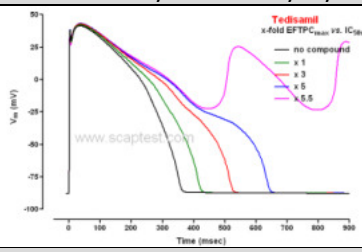
IC index calculation [9]:

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

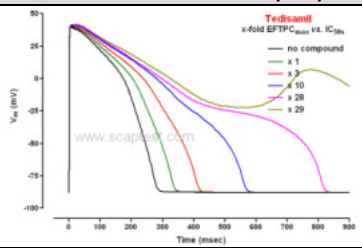
Human epicardial myocytes



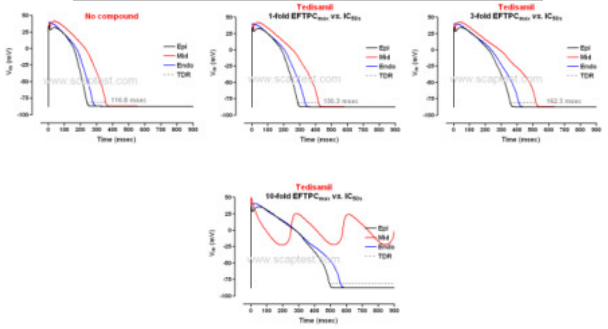
Human midmyocardial myocytes



Human endocardial myocytes

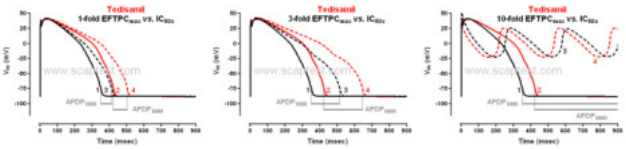


Transmural dispersion of repolarisation



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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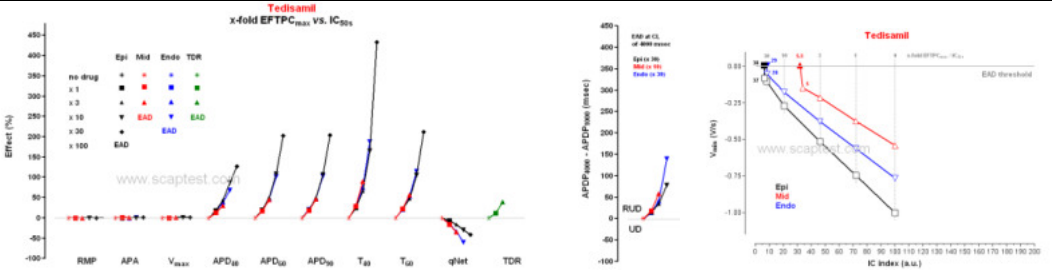

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2. Redfern WS et al. (2003) *Cardiovasc. Res.* **58** : 32-45
3. Kramer J et al. (2013) *Sci.rep.* **3** : 2100
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Abbreviations

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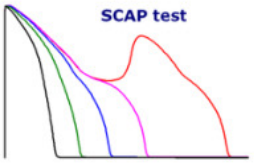

Drug

Telbivudine

Thymidine nucleoside analog used to treat chronic hepatitis B

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 713.9 µM (1.0)
I_{to} : ---- µM (---)
I_{Kr} : 422.7 µM (1.0)
I_{NaL} : ---- µM (---)
I_{Na} : 1095.2µM (1.0)
I_{K1} : ---- µM (---)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ [1]

19.72 µM

TdP risk

Redfern [2] : not reported
Kramer [3] : non-torsadogenic (class 1)
CredibleMeds [4] : not reported
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
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where
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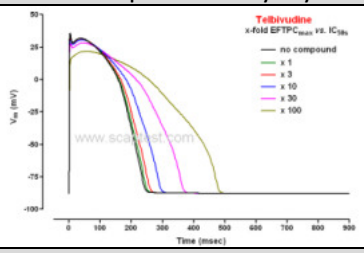
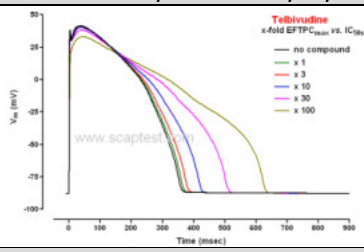
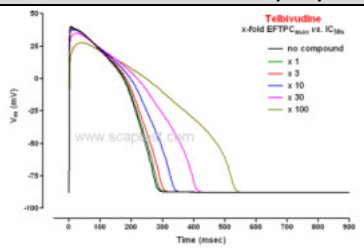
Human epicardial myocytes



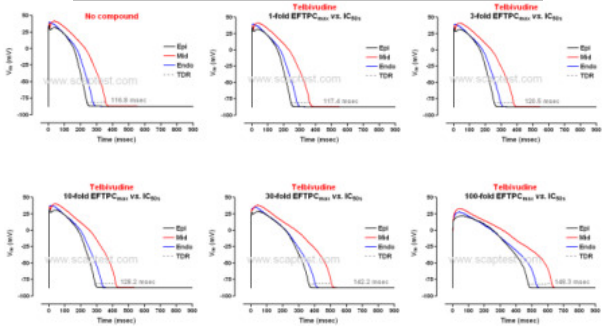
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarisation



Reverse use dependence on midmyocardial myocytes

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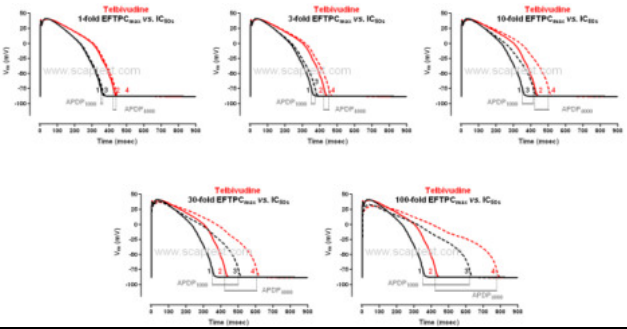

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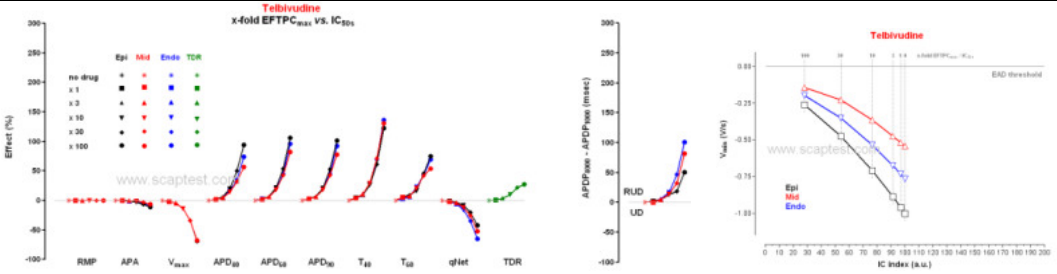

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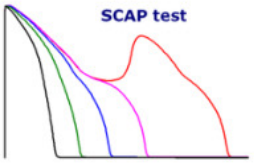

Drug

Terfenadine

Histamine H_1 receptor antagonist used to treat allergy symptoms
no longer marketed wordlwide (Onakpoya et al (2016) *BMC Med.* **14**: 10)

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 0.93 µM (1.8)
I_{Kr} : 0.05 µM (1.15)
I_{Na} : 2.0 µM (1.81)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ [1]

0.009 µM

TdP risk

Redfern [2] : unacceptable TdP risk (class 2)
Kramer [3] : torsadogenic (class 2)
CredibleMeds [4] : known risk of TdP (class 1)
CiPA [5] : intermediate risk of TdP (class 2)
WP [6] : 17/0 (TdP+/TdP-)

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
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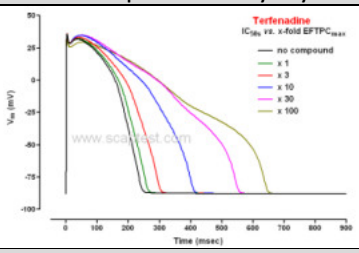
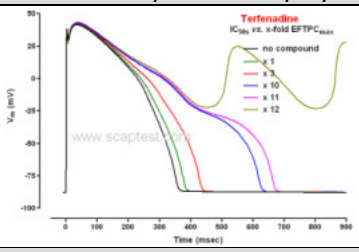
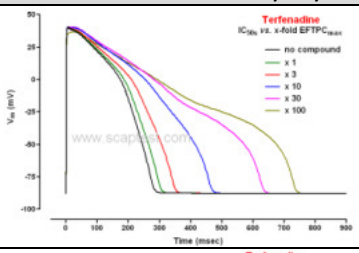


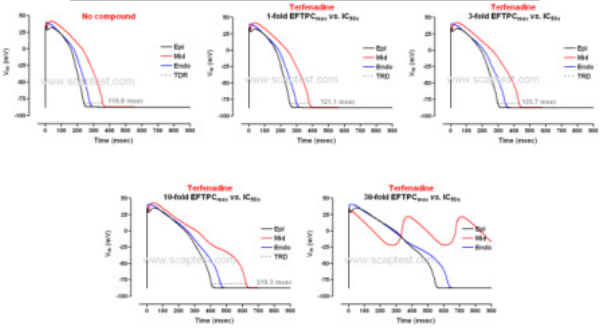
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarisation



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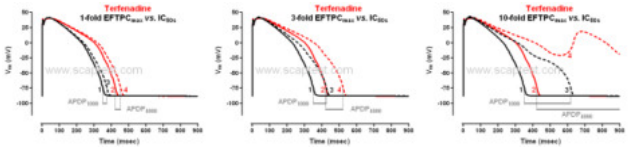

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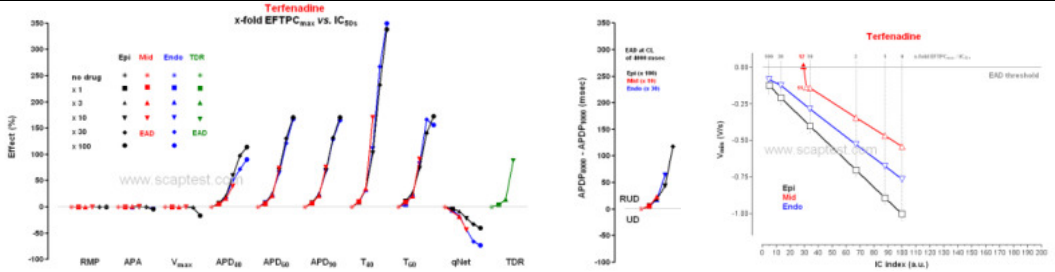

References

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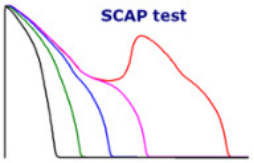

Drug

Terodiline

Voltage-gated Ca^{++} channel ($Ca_v1.2$) blocker and cholinergic receptor antagonist used to treat urinary incontinence
no longer marketed worldwide (Onakpoya et al (2016) *BMC Med.* **14**: 10)

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 4.8 µM (1.01)
I_{Kr} : 0.65 µM (1.02)
I_{Na} : 7.4 µM (1.23)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ [1]

0.145 µM

TdP risk

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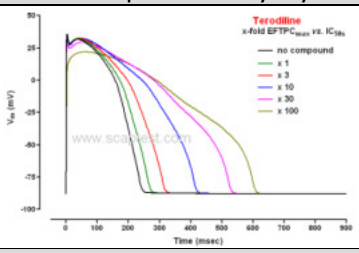
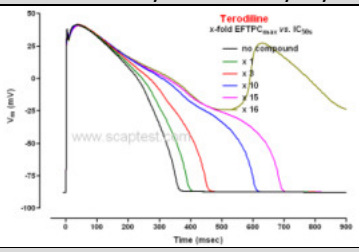
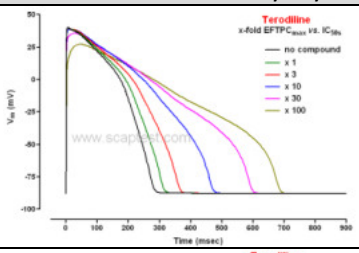


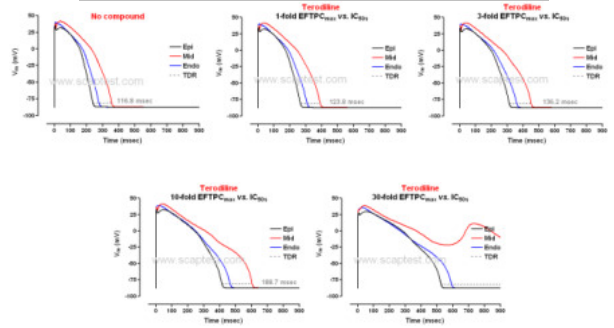
Human midmyocardial myocytes



Human endocardial myocytes

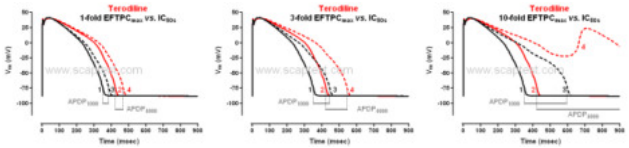


Transmural dispersion of repolarisation

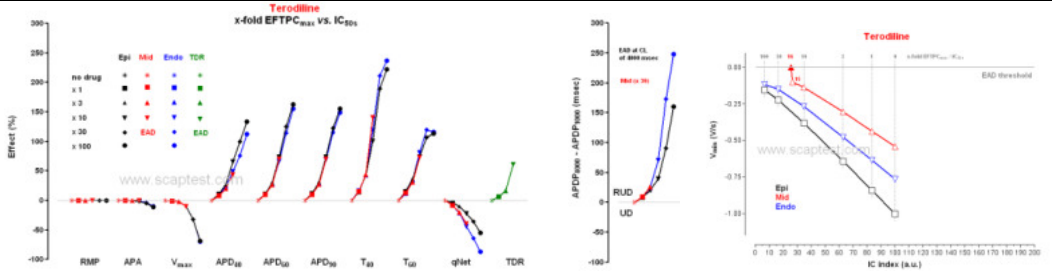


Reverse use dependence on midmyocardial myocytes

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

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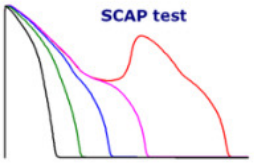


Drug

Thioridazine

Dopamine D_1 and D_2 receptor antagonist used to treat schizophrenia and anxiety
no longer marketed worldwide (Onakpoya et al (2016) *BMC Med.* **14**: 10)

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 3.5 µM (1.35)
I_{Kr} : 0.50 µM (0.98)
I_{Na} : 1.4 µM (1.11)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ [1]

0.98 µM

TdP risk

Redfern [2] : numerous reports of TdP (class 3)
Kramer [3] : torsadogenic (class 2)
CredibleMeds [4] : known risk of TdP (class 1)
CiPA [5] : not reported
WP [6] : 12/0 (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'

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

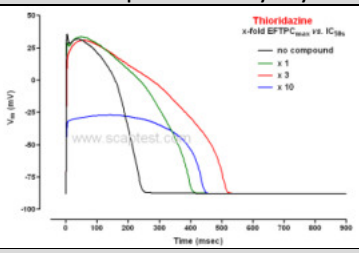
g = maximal conductance of channel 'j'
$g_{control\_j}$ = drug free maximal conductance of channel 'j'
IC50 = 50% of inhibition of a drug for channel 'j'
D= drug concentration (EFTPC for example)
n= hill slope

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

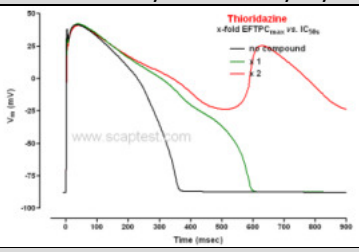
where
$APD_{90}P_x$ = APD_{90} with - APD_{90} without compound at CL x

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}

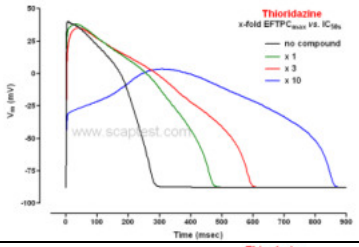
Human epicardial myocytes



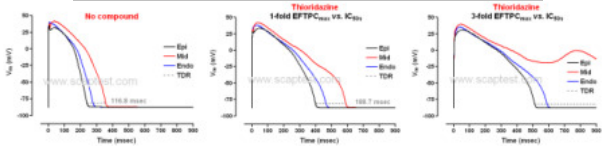
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarisation



Reverse use dependence on midmyocardial myocytes

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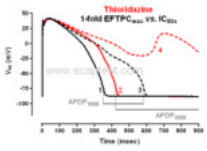
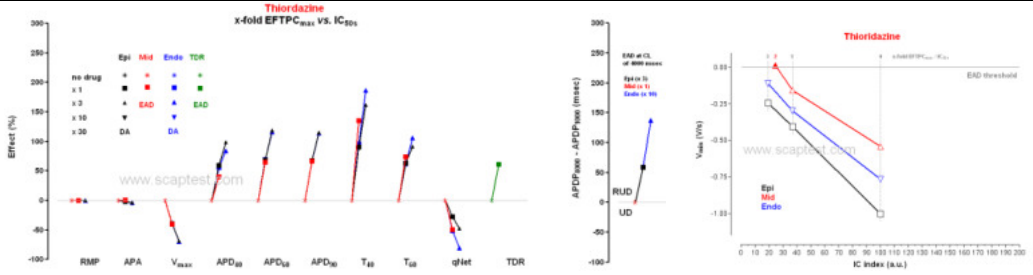


Summary



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Abbreviations

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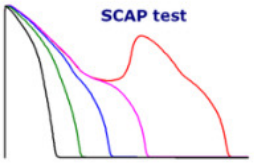

Drug

Tolterodine

Non selective muscarinic receptor antagonist used to treat urinary incontinence

Raw data

IC_{50s} (slope) [1]

I_{CaL} : ---- µM (---)
I_{to} : 12.59 µM (1.0)
I_{Kr} : 0.0126 µM (1.0)
I_{NaL} : ---- µM (---)
I_{Na} : 6.310 µM (1.0)
I_{K1} : ----- µM (---)
I_{Ks}: 79.43 µM (1.0)

$EFTPC_{max}$ [1]

0.000993 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}

$$I_j = g\,O(V - E_{ion})$$

g = 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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  where
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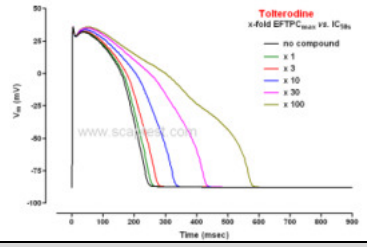
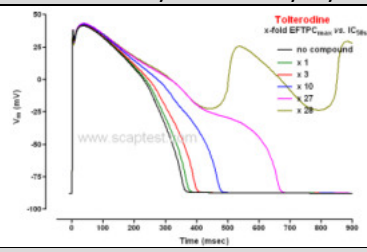
IC index calculation [9]:

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

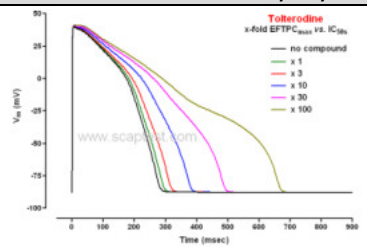
Human epicardial myocytes



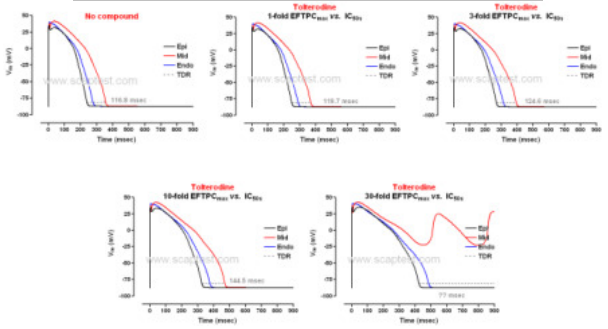
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarisation



Reverse use dependence on midmyocardial myocytes

1 - CL 1000 msec without compound
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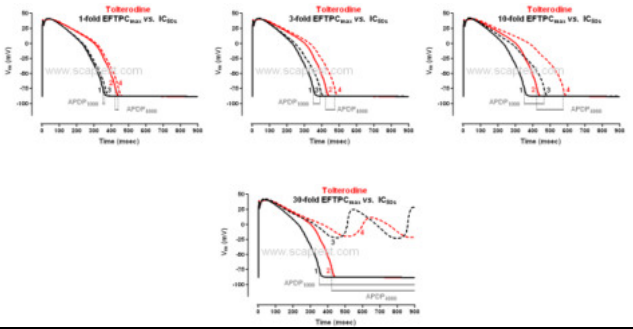
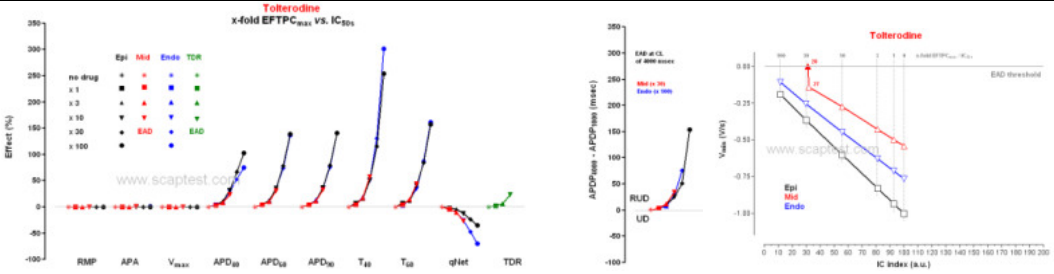


Summary



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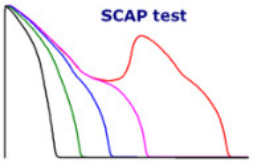

Drug

Vandetanib

Vascular endothelial (VRGFR) or epidermal (EGFR) growth factor receptor antagonist and RET tyrosine kinase inhibitor used to treat medullary thyroid cancer

Raw data

IC_{50s} (slope) [1]

I_{CaL} : ---- µM (---)
I_{Kr} : 0.4 µM (1.0)
I_{Na} : ---- µM (---)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ [1]

0.11 µM

TdP risk

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

Results

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

Simulation conditions:

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- External ionic concentrations (mM):
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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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IC index = (AFKr/((AFNaL+AFCaL)/2))*100
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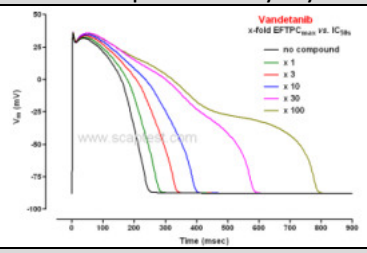
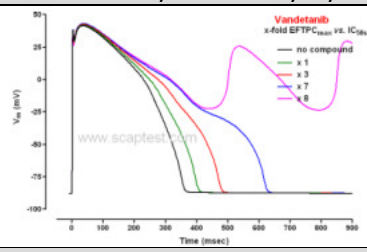
AFKr, AFNaL and AFCaL = active fraction (%) of the I_{Kr}, I_{NaL} and I_{CaL}

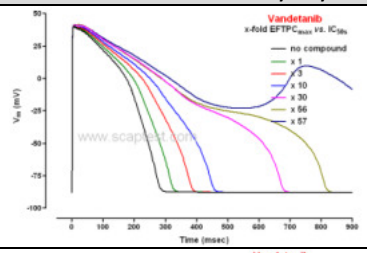
Human epicardial myocytes



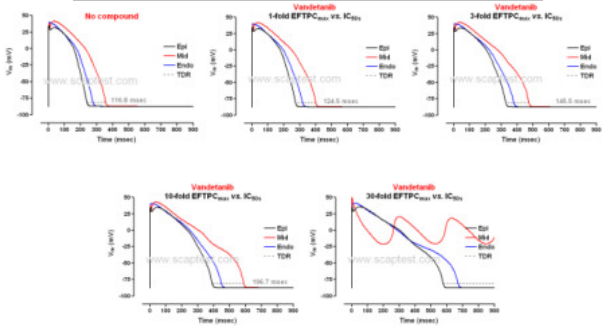
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarisation



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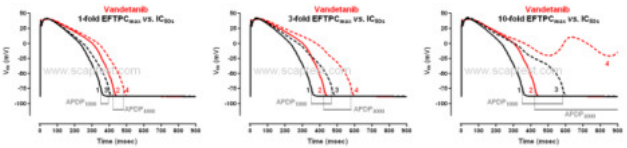
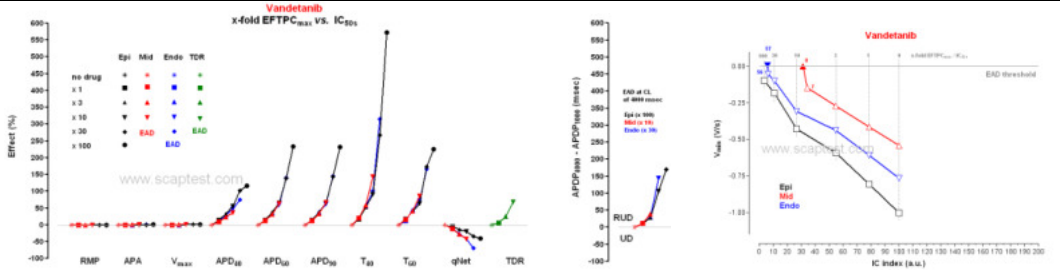


Summary



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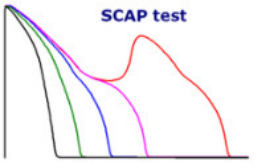
Abbreviations

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_{to}+I_{Na}+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

Vanoxerine

Dopamine transporter antagonist used to treat cocaine addiction

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 0.0162 µM (0.63)
I_{to} : 2.0 µM (1.0)
I_{Kr} : 0.0093 µM (1.11)
I_{NaL} : 0.0852 µM 1.62)
I_{Na} : 0.0346 µM (0.97)
I_{K1} : 98.124 µM (1.0)
I_{Ks} : 2.9 µM (1.0)

$EFTPC_{max}$ [1]

0.00831 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
- 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:

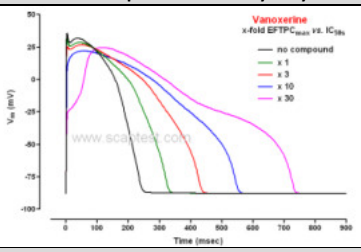
- TDR = APD_{90} mid - APD_{90} epi (at CL of 1000 msec)
- RUD = $APD_{90}P_{4000}$-$APD_{90}P_{1000}$

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

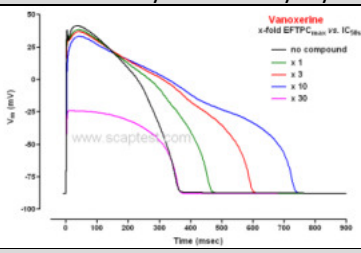
IC index calculation [9]:

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

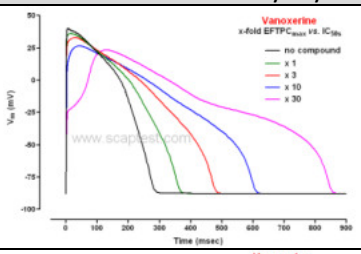
Human epicardial myocytes



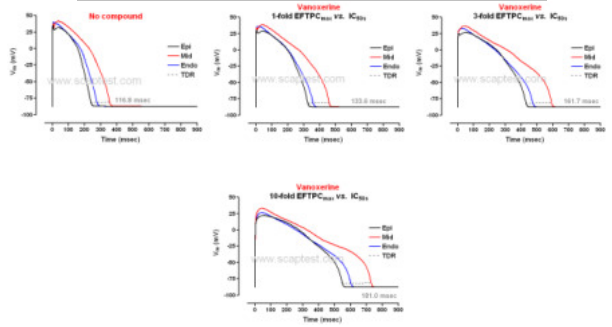
Human midmyocardial myocytes



Human endocardial myocytes

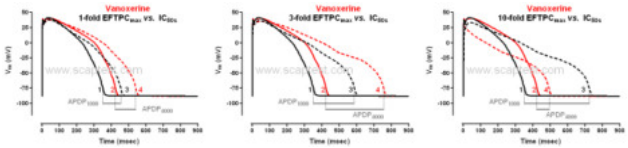


Transmural dispersion of repolarisation

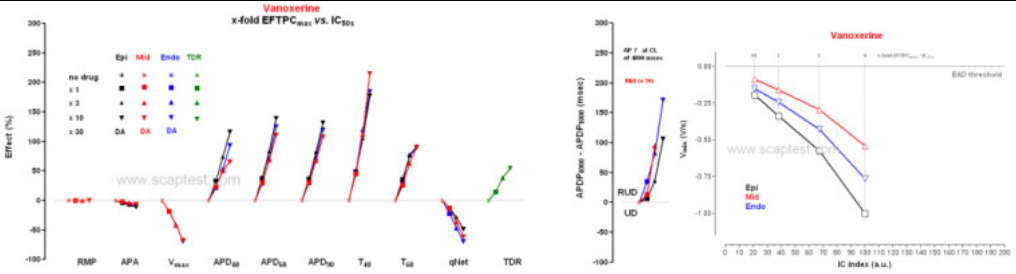


Reverse use dependence on midmyocardial myocytes

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. Obejero-Paz C et al. (2016) *Nature Sci. Rep.* **5**: 17623
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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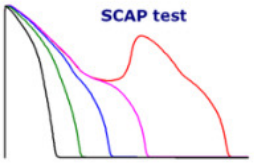

Drug

Vardenafil

Phosphodiesterase PDE-5 inhibitor used to treat erectile dysfunction

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 15.849 µM (1.0)
I_{to} : 79.433 µM (1.0)
I_{Kr} : 31.623 µM (1.0)
I_{NaL} : ---- µM (---)
I_{Na} : 2511.9 µM (1.0)
I_{K1} : ---- µM (---)
I_{Ks} : 630.96 µM (1.0)

$EFTPC_{max}$ [1]

0.004957 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] : 1/2 (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
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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_j = maximal conductance of channel 'j'
O=open probability of channel 'j'
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IC index = (AFKr/((AFNaL+AFCaL)/2))*100
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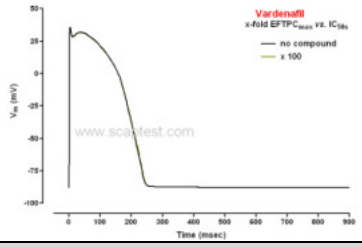
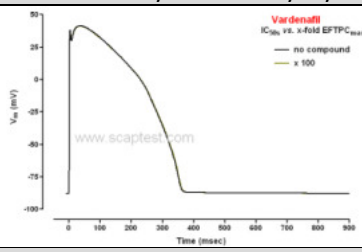
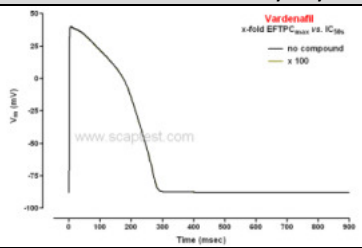
Human epicardial myocytes



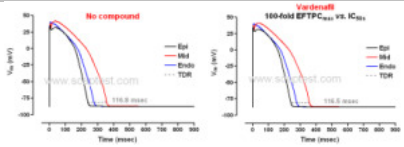
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarisation



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1 - CL 1000 msec without compound
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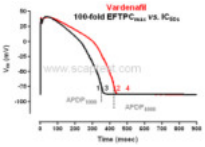

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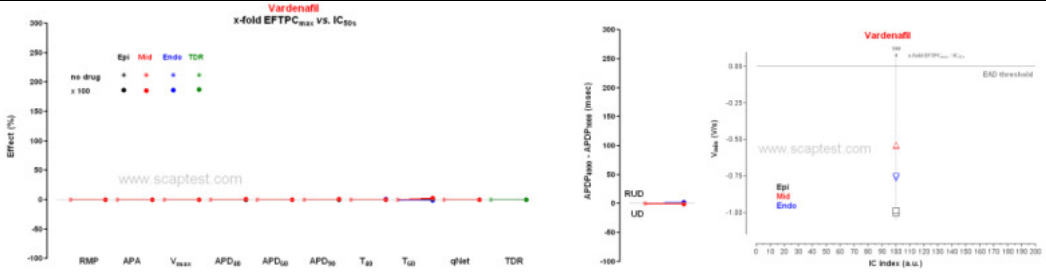

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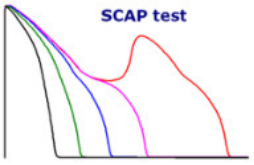

Drug

Verapamil

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

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 0.20 µM (0.80)
I_{Kr} : 0.25 µM (0.89)
I_{Na} : 32.5 µM (1.33)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ [1]

0.088 µM

TdP risk

Redfern [2] : no published report of TdP (class 5)
Kramer [3] : non-torsadogenic (class 1)
CredibleMeds [4] : not classified with TdP risk (class 4)
CiPA [5] : low or no risk of TdP (class 3)
WP [6] : 0/13 (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
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IC index = (AFKr/((AFNaL+AFCaL)/2))*100
where
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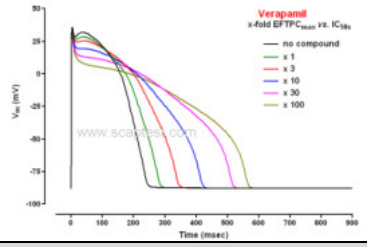
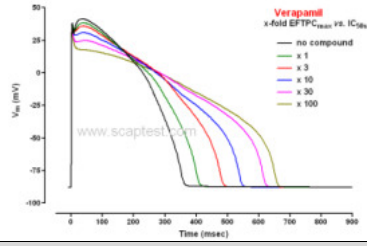
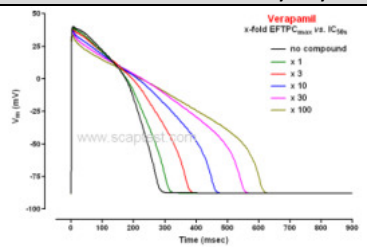
Human epicardial myocytes



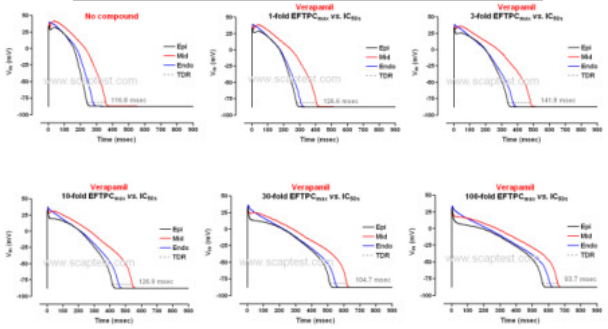
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarisation



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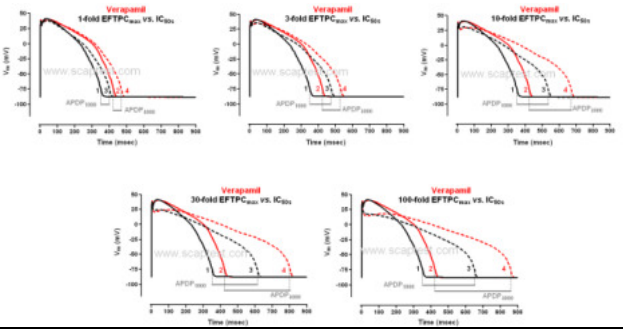
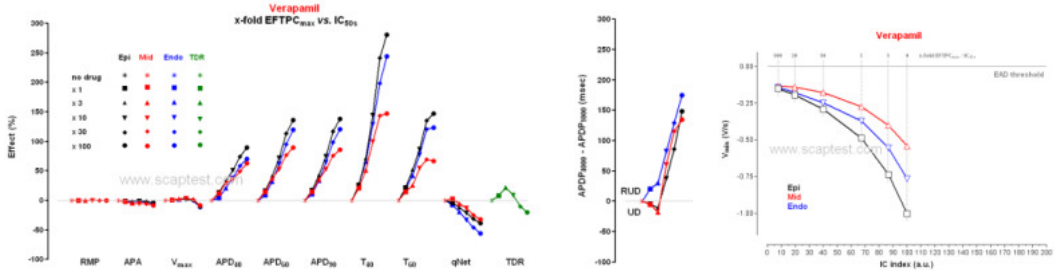


Summary



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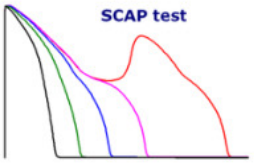

Drug

Vernakalant

Voltage-gated Na^+ channel blocker used as class III antiarrhythmic to treat atrial fibrillation

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 84.0 µM (1.0)
I_{to} : 15.0µM (1.0)
I_{Kr} : 20.0 µM (1.0)
I_{NaL} : ---- µM (---)
I_{Na} : 90.0 µM (1.0)
I_{K1} : 14.0 µM (1.0)
I_{Ks} : ---- µM (---)

$EFTPC_{max}$ [1]

5.24 µM

TdP risk

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

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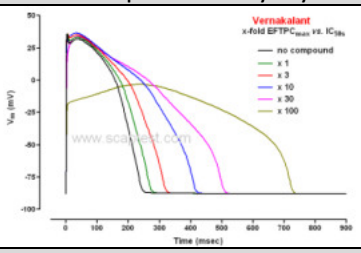
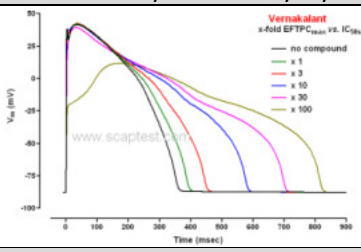
IC index calculation [9]:
IC index = (AFKr/((AFNaL+AFCaL)/2))*100
where
AFKr, AFNaL and AFCaL = active fraction (%) of the I_{Ks}, I_{NaL} and I_{CaL}.

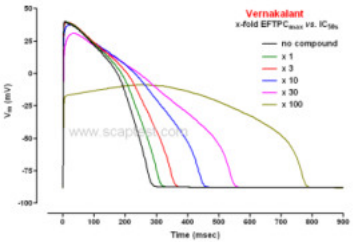
Human epicardial myocytes



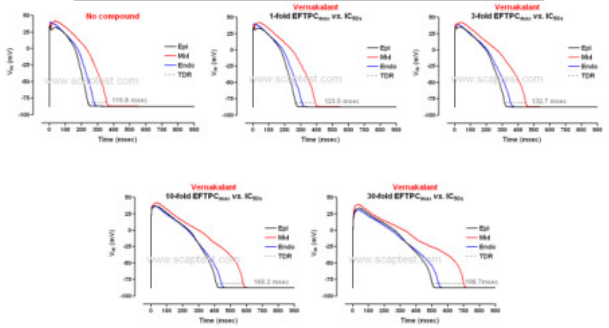
Human midmyocardial myocytes



Human endocardial myocytes

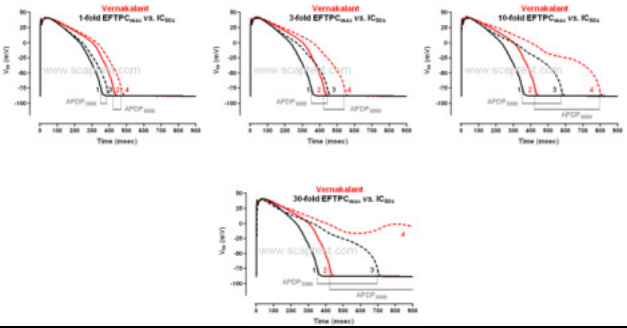


Transmural dispersion of repolarisation

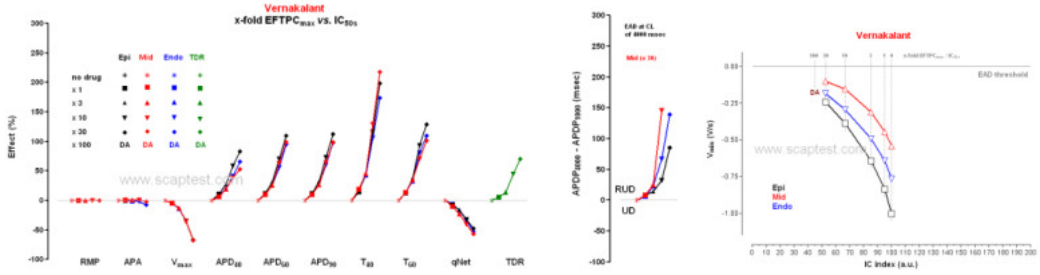


Reverse use dependence on midmyocardial myocytes

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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3. Kramer J et al. (2013) *Sci.rep.* **3** : 2100
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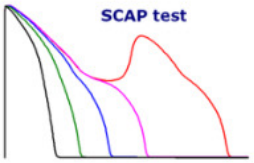
5. CiPA (2016) www.ilsiextra.org/hesi/science/cardiac/cipa/Project
6. Wiśniowska B et al. (2017) *Drug discovery today* **22** : 10-16
7. O'Hara T et al. (2011) *PLoS Comput. Biol.* **7** : e1002061_8
8. Mirams GR et al. (2011) *Cardiovasc. Res.* **91** : 53-61
9. Christophe B & Crumb WJ Jr (2019) *J 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

Voriconazole

14-α sterol demethylase inhibitor used to treat fungal infections

Raw data

IC_{50s} (slope) [1]

I_{CaL} : 414.2 µM (1.0)
I_{Kr} : 490.9 µM (1.0)
I_{Na} : 1550.5 µM (1.0)
I_{Ks} : ---- µM (---)
I_{to} : ---- µM (---)
I_{NaL} : ---- µM (---)
I_{K1} : ---- µM (---)

$EFTPC_{max}$ [1]

7.563 µM

TdP risk

Redfern [2] : not reported
Kramer [3] : torsadogenic (class 2)
CredibleMeds [4] : conditional risk of TdP (class 3)
CiPA [5] : not reported
WP [6] : 5/0 (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)
- 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
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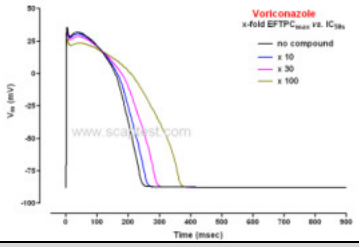
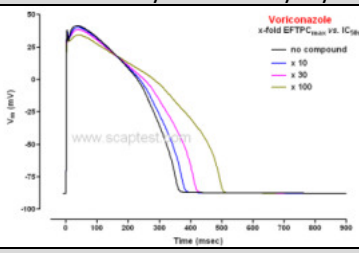
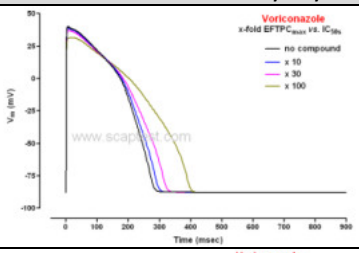
Human epicardial myocytes



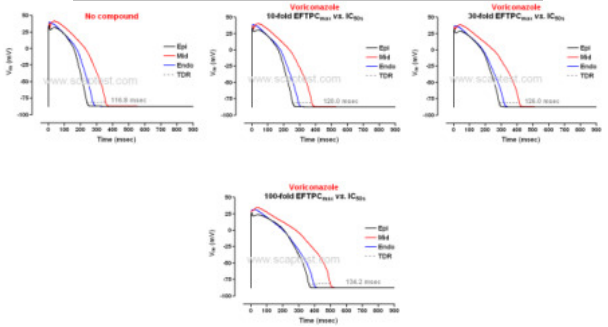
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarisation



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1 - CL 1000 msec without compound
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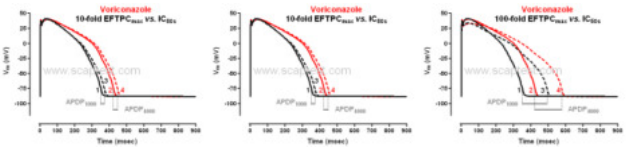
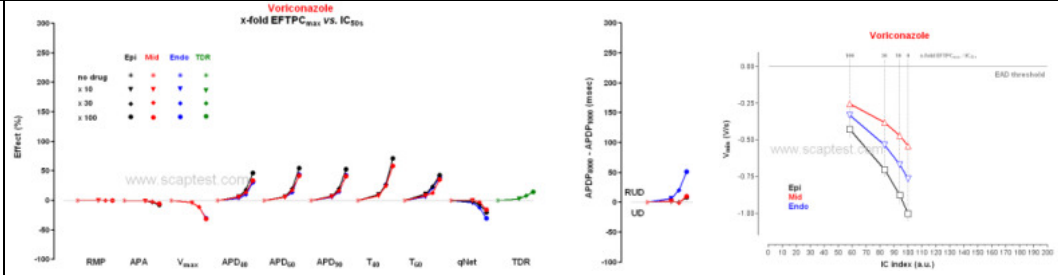


Summary



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2. Redfern WS et al. (2003) *Cardiovasc. Res.* **58** : 32-45
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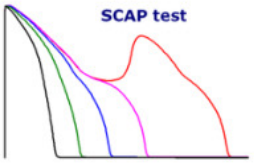

Drug

Ziprasidone

Dopamine D_2 and serotonin 5-HT_{2A} receptor antagonist used to treat schizophrenia or bipolar mania

Raw data

IC_{50s} (slope) [1]

I_{CaL} : ---- µM (---)
I_{to} : ---- µM (---)
I_{Kr} : 0.24 µM (1.0)
I_{NaL} : ---- µM (---)
I_{Na} : 170.0 µM (1.0)
I_{K1} : ---- µM (---)
I_{Ks}: ---- µM (---)

$EFTPC_{max}$ [1]

0.0073 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] : 3/1 (TdP+/TdP-)

Results

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Simulation conditions:
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- Cycle length : 1000 msec
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Effect of drugs on AP [8]:
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$I_j = g_j O(V - E_{ion})$ (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)

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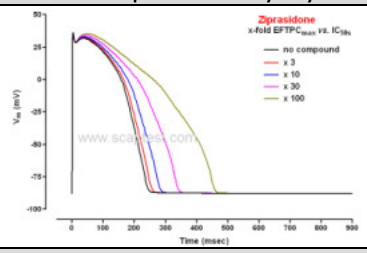
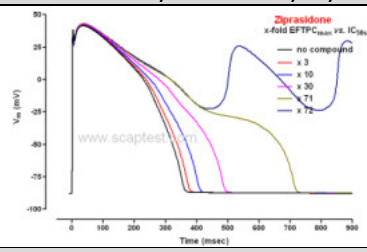
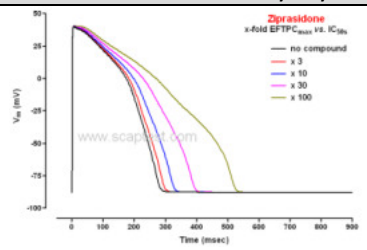


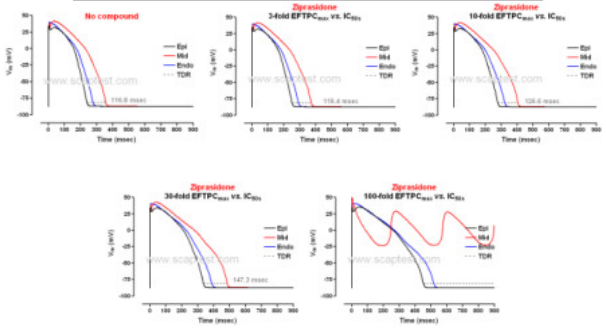
Human midmyocardial myocytes



Human endocardial myocytes



Transmural dispersion of repolarisation



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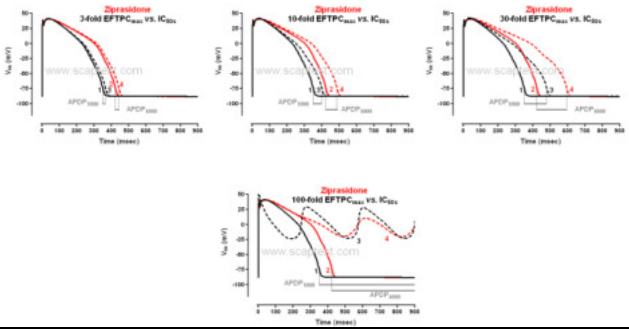

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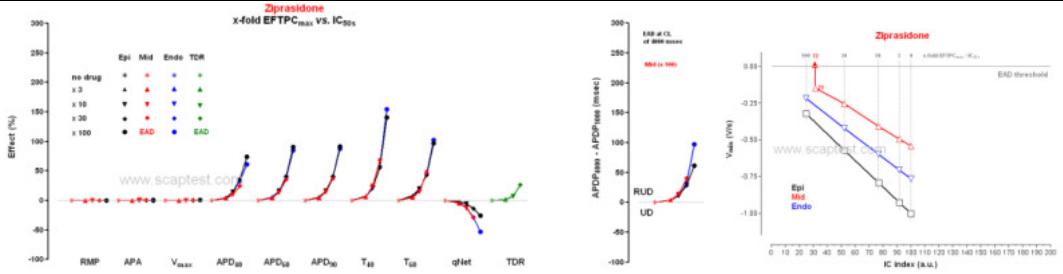

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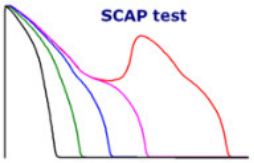

Class 1 (Known TdP risk) §	I_{Kr} #	I_{CaL} #	I_{Na} #	I_{NaL} #	APA ##	V_{max} ##	APD_{90} ##	T_{60} ##	TDR ##	RUD ##	V_{min} ##	IC index €	EAD £
Amiodarone	*	*	*		=	=	=	=	=	=	•	98.0	
Astemizole	***	*	*		=	=	••••	••••	••••	1	••••	32.0	x 36
Azithromycin	***			***	=	=	••••	••••	••••	1	••••	50.6	
Bepridil	****	****	***		◦	◦◦◦◦	••••	••••	••	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
Gatifloxacin	***				=	=	••••	••••	••••	1	••••	32.0	x 7
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
Levofloxacin	***				=	=	••••	••••	••••	1	••••	32.2	x 30
Methadone	***	*	*		=	◦	••••	••••	••••	1	••••	31.3	x 17
Moxifloxacin	****	****	**		◦	◦◦◦	••••	•••	=	••••	••••	14.8	
Ondansetron	***	**		**	=	=	••••	••••	••••	1	••••	30.6	x 14
Pentamidine	*				=	=	•	••••	••	◦	=	99.9	
Pimozide	***	*	*		=	=	•••	•••	••	•••	••••	45.6	
Procainamide	****	****	****		²	²	²	²	²	²	²	8.7	
Quinidine	****	**	*		=	◦	••••	••••	••••	1	••••	27.4	x 0.8
Sertindole	***	*	*		=	=	••••	••••	••••	••••	••••	32.2	x 31
Sotalol	****	****	*		◦	◦	••••	•••	◦◦	••••	••••	23.7	
Sparfloxacin	****	***	*		=	=	••••	••••	••••	1	••••	18.9	
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

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

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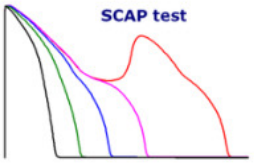
€ : IC index: Ion Channel inhibition index calculated at an $EFTPC_{max}/EC_{50s}$ ratio of 100-fold in absence of EAD or at the last $EFTPC_{max}/EC_{50s}$ ratio (x-fold-1) before the presence of an EAD (see page 4 for calculation)

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

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

[2] Depolarisation abnormality



Class 2 (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	
Clozapine	***	***	**		◦	◦◦	••••	•••	••	••••	••••	37.6	
Dasatinib	*	*	*		=	=	•	=	=	•	••	91.0	
Desipramine	****	****	****		[2]	[2]	[2]	[2]	[2]	[2]	[2]	20.2	
Dolasetron	***		**		=	◦◦	••••	••••	••••	[1]	••••	32.7	x 35
Imipramine	***	***	***		=	◦◦◦◦	••••	••••	•••	••••	••••	33.9	
Ketanserin	***				=	=	••••	••••	••••	[1]	••••	31.8	x 78
Lapatinib	***	*	*		=	=	••••	••••	••••	[1]	••••	31.9	x 55
Lopinavir	****	****			◦	•	••••	••••	•••	[1]	••••	7.1	
Nicardipine	****	****	***		◦◦	◦◦◦	••••	•	◦◦	••••	••••	30.4	
Nilotinib	***	*	*		=	=	••••	••••	••••	[1]	••••	29.5	x 17
Ofloxacin	**				=	=	••	••	••	••	•••	62.0	
Paliperidone	***	*	*		=	=	••••	••••	••••	[1]	••••	32.9	x 25
Palonosetron	*	*	*		=	=	•	•	•	•	••	81.1	
Saquinavir	**	****	***		◦	◦◦◦	•	◦	◦◦◦◦	◦	•••	111	
Sunitinib	***	*	*		=	=	•••	•••	••	•••	•••	48.7	
Tamoxifen	***				=	=	••••	••••	••••	[1]	••••	31.7	x 94
Tolterodine	***		*		=	=	••••	••••	••••	[1]	••••	32.0	x 28
Vardenafil	*	*	*		=	=	=	=	=	=	=	100	

§ : Crediblemeds classification of compound TdP risk

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

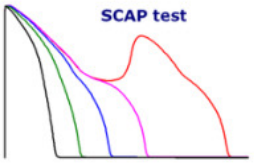
: Effect measured on the midmyocardial myocyte at an $EFTPC_{max}/EC_{50s}$ ratio of 100-fold in absence of EAD or at the last $EFTPC_{max}/EC_{50s}$ ratio (x-fold-1) before the presence of an EAD: -5 to 5 % (=), -5 to -20 % (◦), -20 to -40 % (◦◦), -40 to -60 % (◦◦◦), > -60 % (◦◦◦◦), 5 to 20 % (•), 20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

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

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

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

[2] Depolarisation abnormality



Class 3 (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	
Diltiazem	**	****	**		◦	◦◦	••	•	◦◦	•	•••	101	
Diphenhydramine	**	*	*		=	◦	••	••	•	•	•••	60.9	
Famotidine	*				=	=	=	=	=	=	=	98.6	
Fluoxetine	**	**	*		=	=	••	••	•	•	•••	67.1	
Fluvoxamine	****	****	**		◦	◦◦	••••	•••	=	••••	••••	21.8	
Hydroxyzine	***	*	***	*	=	◦◦◦◦	••••	••••	••••	[1]	••••	34.4	x 90
Ivabradine	**	*	*		=	=	•	••	•	•	••	73.3	
Ketoconazole	***		*		=	◦	••••	••••	••••	[1]	••••	32.2	x 43
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	***		*		=	=	••••	••••	••••	[1]	••••	31.6	x 72

§ : Crediblemeds classification of compound TdP risk

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

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

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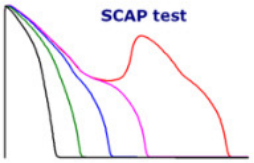

Class 4 (No TdP risk) §	I_{Kr} #	I_{CaL} #	I_{Na} #	I_{NaL} #	APA ##	V_{max} ##	APD_{90} ##	T_{60} ##	TDR ##	RUD ##	V_{min} ##	IC index €	EAD £
Ambrisentan	*	*	*		=	=	=	=	=	=	=	97.7	
Amlodipine	****	****	***		◦◦	◦◦◦◦	••••	•	◦◦	••••	••••	26.3	
Aspirin	*				=	=	=	=	=	=	=	99.2	
Atenolol	*				=	=	•	•	=	=	•	91.4	
Ceftriaxone	****	****	****		◦◦	◦◦◦◦	••••	•	◦◦◦◦	•••	••••	30.4	
Cetirizine	*				=	=	=	=	=	=	=	97.7	
Chlorpheniramine	*				=	=	=	•	=	=	•	91.5	
Darifenacin	***	*	*		=	◦	••••	••••	••••	••••	••••	36.9	
Darunavir	**		***		=	◦◦◦	••	••	•	•	••	77.4	
Desvenfalaxine	***		***		=	◦◦◦◦	•••	•••	••	••••	•••	49.4	
Diazepam	*	*	*		=	=	=	=	=	=	=	101	
Doxorubicin	**				=	=	•••	••	••	••	•••	68.3	
Duloxetine	**	**	*		=	◦	•	•	=	=	••	91.1	
Eltrombopag	***		*		=	=	••••	••••	••••	[1]	••••	33.3	x 12
Everolimus	*		*		=	=	=	=	=	=	=	98.7	
Fexofenadine	*				=	=	•	=	•	=	•	93.6	
Gefitinib	***				=	=	••••	••••	••••	[1]	••••	32.5	x 26
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	
Nebivolol	**		*		=	=	•	•	•	•	••	77.1	
Nifedipine	*	****	*		◦	=	◦	•	◦	••	•••	190	
Oxybutynin	*	*			=	=	=	=	=	=	=	100	
Phenytoin	***	****	****		[2]	[2]	[2]	[2]	[2]	[2]	[2]	48.1	
Propranolol	*	*			=	=	•	•	=	=	•	91.2	
Raltegravir	*	**	*		=	◦	=	=	=	=	•	103	
Ribavirin	***	****	**		◦	◦◦◦	•••	••	◦	•••	••••	43.6	
Sildenafil	*	*	*		=	=	•	•	•	•	•	84.4	
Silodosin	*	*	*		=	=	•	•	=	•	•	89.5	
Tadalafil	*		*		=	◦	•	•	•	•	•	88.0	
Verapamil	****	****	*		◦	◦	••••	••••	◦	••••	••••	7.7	

§ : Crediblemeds classification of compound TdP risk

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

: Effect measured on the midmyocardial myocyte at an $EFTPC_{max}/EC_{50s}$ ratio of 100-fold in absence of EAD or at the last $EFTPC_{max}/EC_{50s}$ 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 $EFTPC_{max}/EC_{50s}$ ratio of 100-fold in absence of EAD or at the last $EFTPC_{max}/EC_{50s}$ ratio (x-fold-1) before the presence of an EAD (see page 4 for calculation)

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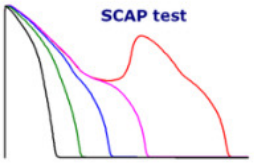

Class 5 (not reported) [§]	I_{Kr} [#]	I_{CaL} [#]	I_{Na} [#]	I_{NaL} [#]	APA [##]	V_{max} [##]	APD_{90} [##]	T_{60} [##]	TDR [##]	RUD [##]	V_{min} [##]	IC index [€]	EAD [£]
Ajmaline	***	*	**		=	◦◦	••••	••••	••••	1	••••	31.6	x 93
Almokalant	***				=	=	••••	••••	••••	1	••••	31.9	x 48
Alvimopan	*	*	*		=	=	=	=	=	•	=	109	
Azimilide	***				=	=	••••	••••		1	••••	31.6	x 13
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	
Levosimendan	*	*	*		=	=	=	•	=	=	•	95.6	
Maraviroc	**		*		=	=	•	•	•	•	••	78.4	
Mibefradil	**	***	*		◦	=	•	•	◦◦	◦	••	101	
Nimodipine	*	**			=	=	=	◦	=	◦◦	•	129	
Nisoldipine	*	*			=	=	=	=	=	=	=	106	
Nitrendipine	*	****	*		◦	=	◦	◦	◦◦	◦	•	173	
Omecamtiv mecarb	*	*	*		=	◦	•	•	•	•	•	84.9	
Pentobarbital	**	***	*		◦	◦	•	=	◦	◦◦	•	111	
Prenylamine	***	*	*		=	◦	••••	••••	••••	1	••••	28.9	x 51
Primidone	**		***		=	◦◦◦◦	••	••	•	••	•••	62.0	
Ritonavir	****	****		***	◦	•	••••	••••	◦◦	••••	••••	65.4	
Rufinamide		****			◦	•	◦	•	=	•	••	192	
Sitaglitin	**	**	*		=	=	•	=	•	=	•	90.2	
Tedisamil	***				=	=	••••	••••	••••	1	••••	34.0	x5.5
Telbivudine	****	***	***		◦	◦◦◦◦	••••	•••	••	••••	••••	27.9	
Vanoxerine	****	****	****	****	[2]	[2]	[2]	[2]	[2]	[2]	[2]	13.3	
Vernakalant	****	****	****	****	[2]	[2]	[2]	[2]	[2]	1	[2]	44.8	

§ : Crediblemeds classification of compound TdP risk
§§ : Drug not reported in classes 1, 2, 3 or 4 but drug to avoid in congenital long QT
# : Active fraction of I_{Kr}, I_{CaL}, I_{Na} or I_{NaL} cardiac current calculated at an $EFTPC_{max}/EC_{50s}$ ratio of 100-fold in absence of EAD or at the last $EFTPC_{max}/EC_{50s}$ ratio (x-fold-1) before the presence of an EAD: 0 to 20 % (****), 20 to 50 % (***), 50 to 80 % (**) and 80 to 100 % (*)
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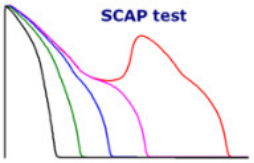
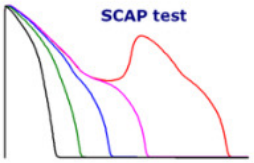


Drugs:

Ajmaline	6	Dolasetron	44	Lidocaine	82	Propafenone	120
Alfuzosin	7	Domperidone	45	Linezolid	83	Propranolol	121
Almokalant	8	Donepezil	46	Lopinavir	84	Quetiapine	122
Alvimopan	9	Doripenem	47	Loratadine	85	Quinidine	123
Ambrisentan	10	Doxorubicin	48	Maraviroc	86	Quinine	124
Amiodarone	11	Dronedarone	49	Mefloquine	87	Raltegravir	125
Amitriptyline	12	Droperidol	50	Methadone	88	Ranolazine	126
Amlodipine	13	Duloxetine	51	Metoprolol	89	Ribavirin	127
Aspirin	14	E-4031	52	Metronidazole	90	Risperidone	128
Astemizole	15	Ebastine	53	Mexiletine	91	Ritonavir	129
Atenolol	16	Eltrombopag	54	Mibefradil	92	Rufinamide	130
Azimilide	17	Encainide	55	Milrinone	93	Saquinavir	131
Azithromycin	18	Erythromycin	56	Mitoxantrone	94	Sertindole	132
Bepridil	19	Etravirine	57	Moxifloxacin	95	Sertraline	133
Ceftriaxone	20	Everolimus	58	Nebivolol	96	Sildenafil	134
Cetirizine	21	Famotidine	59	Nelfinavir	97	Silodosin	135
Chloroquine	22	Fexofenadine	60	Nicardipine	98	Sitagliptin	136
Chlorpheniramine	23	Flecainide	61	Nifedipine	99	Solifenacin	137
Chlorpromazine	24	Fluoxetine	62	Nilotinib	100	Sotalol	138
Cibenzoline	25	Fluvoxamine	63	Nimodipine	101	Sparfloxacin	139
Cilostazol	26	Gatifloxacin	64	Nisoldipine	102	Sunitinib	140
Ciprofloxacin	27	Geftinib	65	Nitrendipine	103	Tadalafil	141
Cisapride	28	Halofantrine	66	Ofloxacin	104	Tamoxifen	142
Citalopram	29	Haloperidol	67	Olanzapine	105	Tedisamil	143
Clarithromycin	30	Hydroxychloroquine	68	Omecamtiv mecarbil	106	Telbuvidine	144
Clozapine	31	Hydroxyzine	69	Ondansetron	107	Terfenadine	145
Darifenacin	32	Ibutilide	70	Oxybutynin	108	Terodiline	146
Darunavir	33	Imipramine	71	Paliperidone	109	Thioridazine	147
Dasatinib	34	Ivabradine	72	Palonosetron	110	Tolterodine	148
Deferasirox	35	Ketanserin	73	Paroxetine	111	Vandetanib	149
Desipramine	36	Ketoconazole	74	Pentamidine	112	Vanoxerine	150
Desvenlafaxine	37	Lacosamide	75	Pentobarbital	113	Vardenafil	151
Diazepam	38	Lamivudine	76	Phenytoin	114	Verapamil	152
Diltiazem	39	Lamotrigine	77	Pimozide	115	Vernakalant	153
Diphenylhydramine	40	Lapatinib	78	Piperacillin	116	Voriconazole	154
Disopyramide	41	Levocetirizine	79	Prenylamine	117	Ziprasidone	155
Dobutamine	42	Levofloxacin	80	Primidone	118		
Dofetilide	43	Levosimendan	81	Procainamide	119		

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. 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. (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