

3rd Annual Predictive Toxicology
half day interactive pre-conference workshop

Tox IVIVE - inter-individual variability matters!

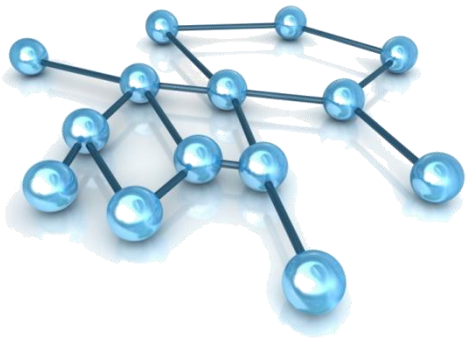
ToxComp platform – case study

Sebastian Polak



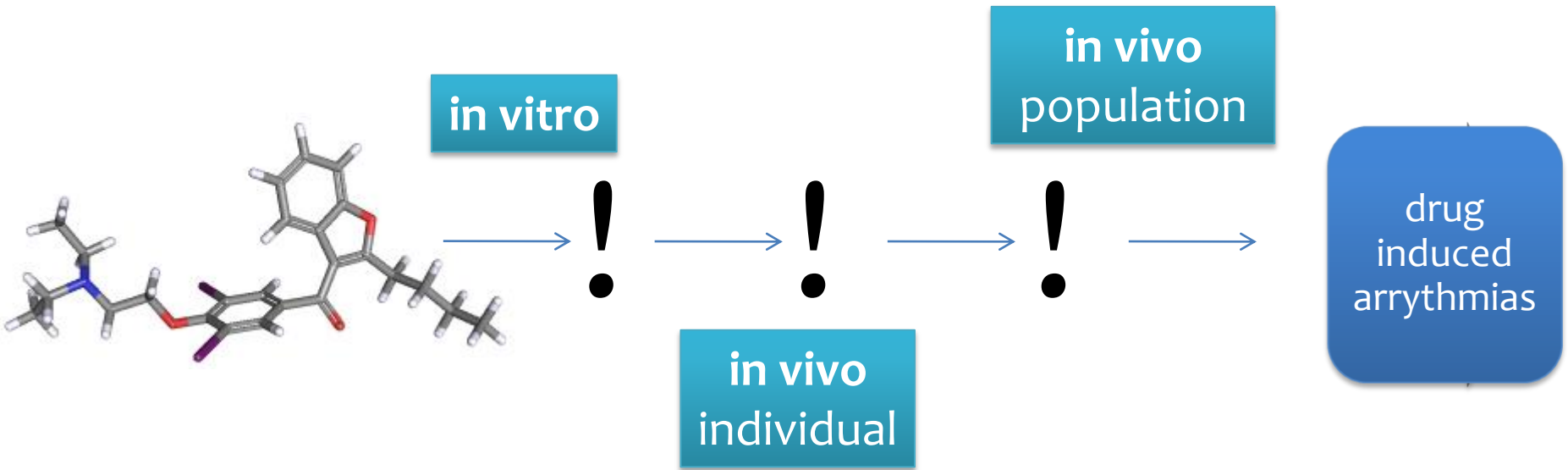
Unit of Pharmacoepidemiology and
Pharmacoeconomics
Jagiellonian University Medical College

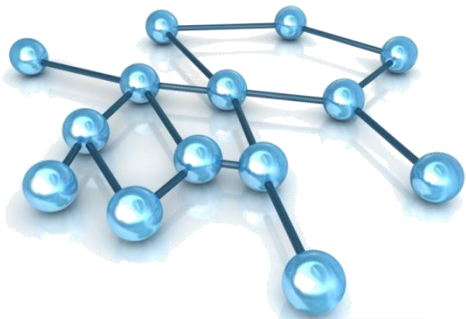




proarrhythmic potency assessment

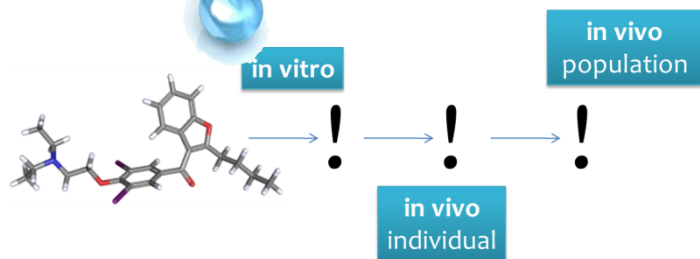
in silico – in vitro – in vivo extrapolation





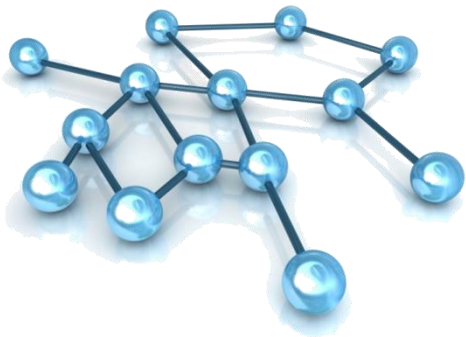
proarrhythmic potency assessment

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project financed by the Polish National Center for Research and Development LIDER project number LIDER/02/187/L-1/09





proarrhythmic potency assessment

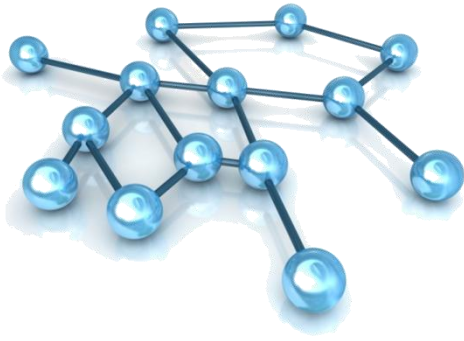
in silico – in vitro – in vivo extrapolation

We assessed the effect on QTc of oral domperidone and ketoconazole, alone and in combination. Ketoconazole, a CYP3A inhibitor, tripled domperidone concentrations, whilst domperidone did not affect ketoconazole concentrations. Domperidone and ketoconazole, alone and in combination, increased QTc significantly in men, and there was a positive correlation between increased QTc and concentrations of domperidone and ketoconazole in both sexes.

Pharmacokinetic interaction between domperidone and ketoconazole leads to QT prolongation in healthy volunteers: a randomized, placebo-controlled, double-blind, crossover study

Malcolm J Boyce, Kathy J Baisley, Steven J Warrington

Hammersmith Medicines Research, Cumberland Avenue, London, NW10 7ES

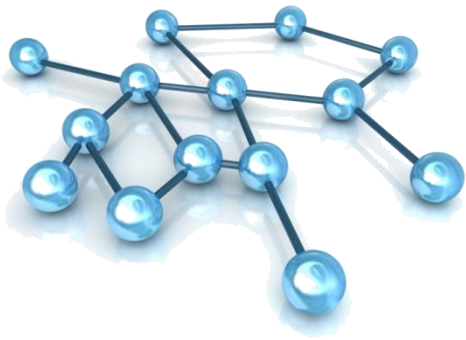


proarrhythmic potency assessment

in silico – in vitro – in vivo extrapolation

CLINICAL INFORMATION

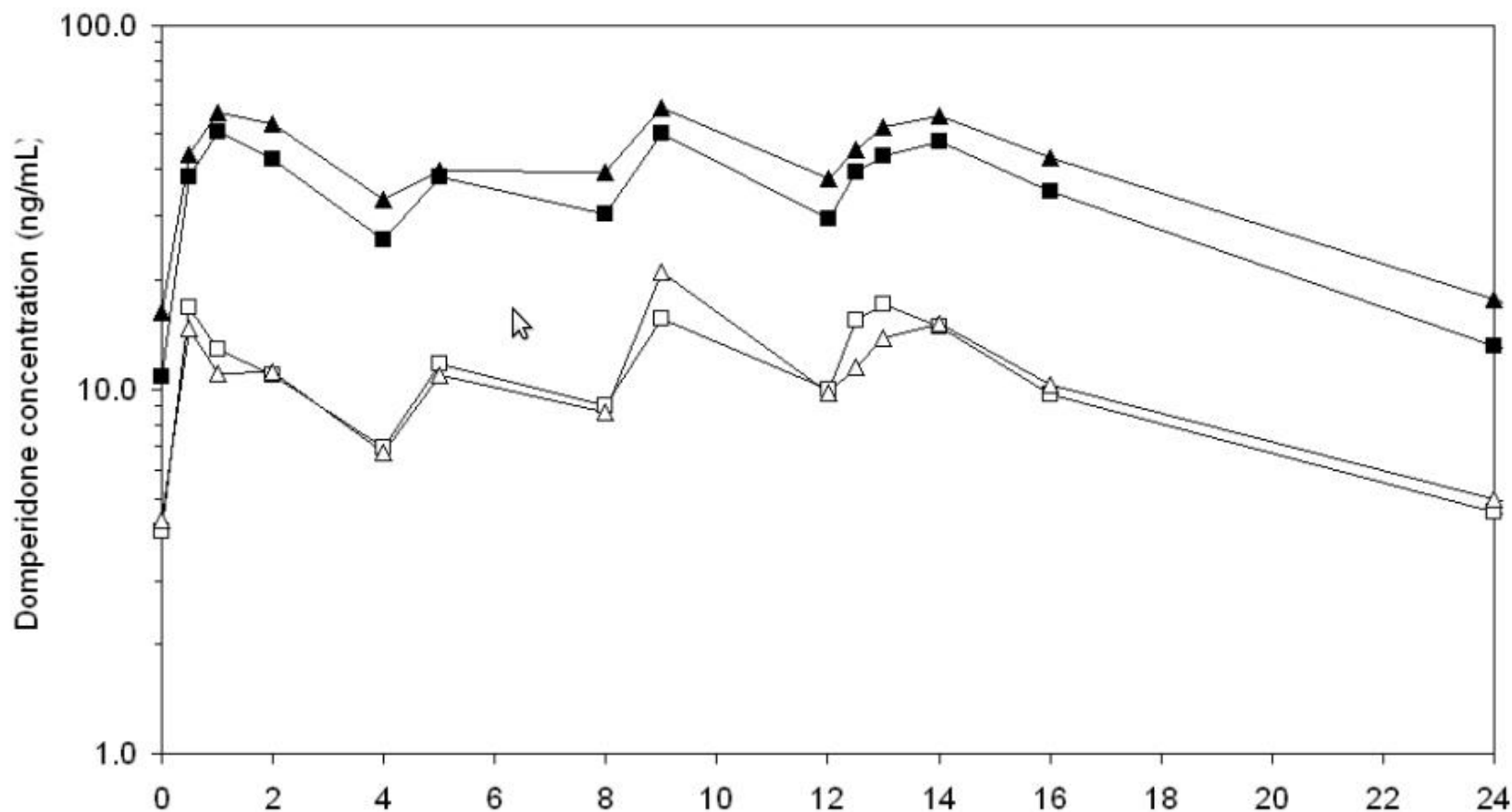
- a randomised, placebo-controlled, double-blind, crossover study
- healthy subjects (14 men, 10 women; age 18–39 y; mean weight 73.5 kg, range 53.8–98.8 kg; 23 Europid ,1 Afro-Caribbean)
- received orally, for 7 days each: placebo; domperidone 10 mg, 4 doses daily, at 4-hour intervals; ketoconazole 200 mg 12-hourly; and domperidone and ketoconazole together

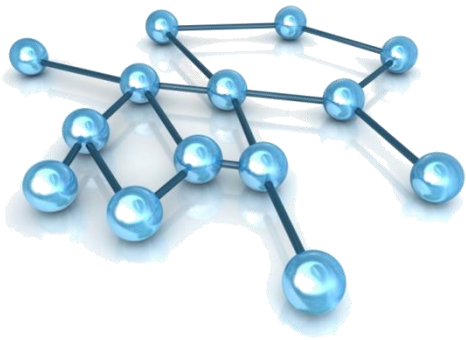


proarrhythmic potency assessment

in silico – in vitro – in vivo extrapolation

CLINICAL INFORMATION

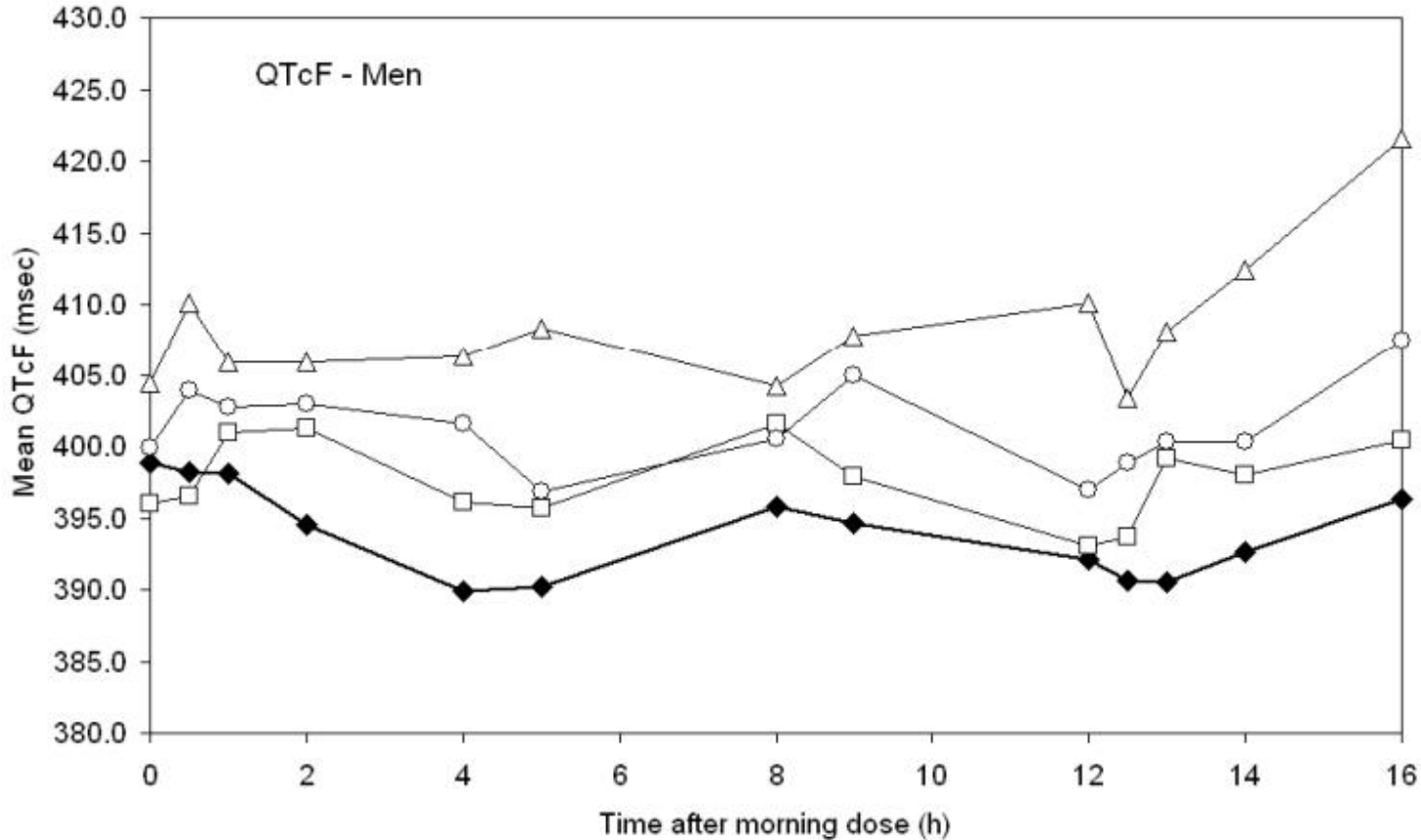


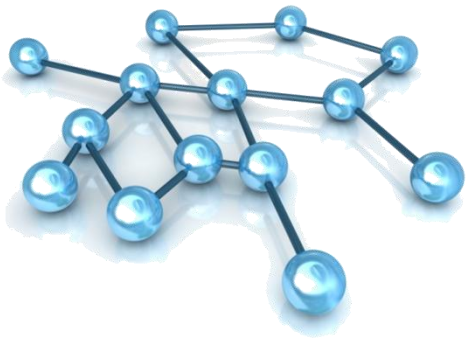


proarrhythmic potency assessment

in silico – in vitro – in vivo extrapolation

CLINICAL INFORMATION



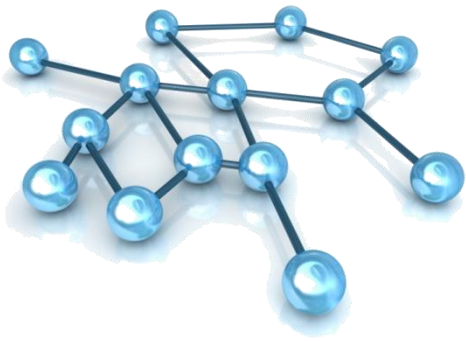


proarrhythmic potency assessment

in silico – in vitro – in vivo extrapolation

CLINICAL INFORMATION

Parameter	Single	Combination	Ratio (90% CI) ¹
Domperidone (ng/mL)			
AUC _{0–24,ss}	249.0 (65.33)	878.1 (267.7)	3.57 (3.31–3.86) *
C _{max,ss}	23.48 (7.35)	67.85 (21.11)	2.93 (2.65–3.25) *
C _{min,ss}	4.23 (1.12)	13.23 (4.80)	3.12 (2.83–3.43) *
C _{avg,ss}	10.38 (2.73)	36.60 (11.16)	3.57 (3.31–3.86) *
Vd/f _{ss} (L)	788.1 (336.0)	191.6 (85.0)	0.24 (0.22–0.26) *
Cl/f _{ss} (mL/min)	1005.7 (314.8)	321.9 (91.5)	0.32 (0.29–0.34) *
t _{1/2β,ss}	8.99 (1.24)	6.81 (1.38)	0.75 (0.71–0.79) *
t _{max} [†]	9.0 (0.5–14.0)	5.0 (0.5–14.1)	

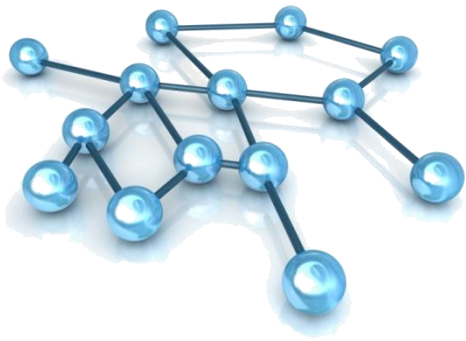


proarrhythmic potency assessment

in silico – in vitro – in vivo extrapolation

CLINICAL INFORMATION

Time	Domperidone		Ketoconazole		Combination	
	mean difference (95% CI)	p-value	mean difference (95% CI)	p-value	mean difference (95% CI)	p-value
Men						
0 h	-2.32 (-10.63–5.99)	0.58	3.06 (-5.11–11.24)	0.46	7.17 (-1.14–15.48)	0.09
0.5 h	-1.15 (-9.46–7.16)	0.79	7.53 (-0.67–15.74)	0.07	13.43 (5.12–21.74)	0.002
1 h	3.32 (-4.99–11.63)	0.43	6.58 (-1.60–14.76)	0.11	9.34 (1.04–17.65)	0.03
2 h	7.23 (-1.07–15.54)	0.09	10.52 (2.34–18.70)	0.01	12.96 (4.65–21.27)	0.002
4 h	6.73 (-1.57–15.04)	0.11	13.60 (5.43–21.78)	0.001	18.10 (9.77–26.44)	<0.001
5 h	5.94 (-2.37–14.25)	0.16	8.56 (0.38–16.73)	0.04	19.58 (11.27–27.88)	<0.001
8 h	6.27 (-2.03–14.58)	0.14	6.57 (-1.60–14.75)	0.11	10.05 (1.73–18.37)	0.02
9 h	3.76 (-4.55–12.07)	0.37	12.22 (4.05–20.39)	0.003	14.72 (6.41–23.03)	<0.001

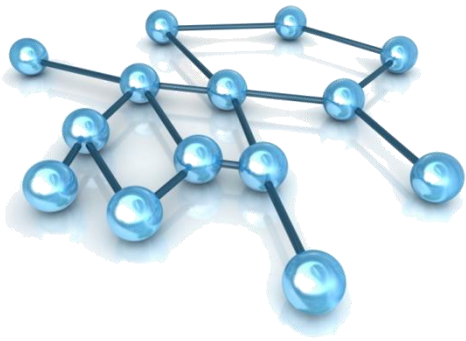


proarrhythmic potency assessment

in silico – in vitro – in vivo extrapolation

CLINICAL INFORMATION

Time	Domperidone		Ketoconazole		Combination	
	mean difference (95% CI)	p-value	mean difference (95% CI)	p-value	mean difference (95% CI)	p-value
Women						
0 h	-3.10 (-11.77–5.56)	0.48	-3.62 (-12.30–5.07)	0.41	-3.48 (-12.14–5.19)	0.43
0.5 h	-2.16 (-10.85–6.54)	0.63	-4.25 (-12.93–4.44)	0.34	1.39 (-7.46–10.23)	0.76
1 h	-2.61 (-11.29–6.06)	0.55	0.07 (-8.61–8.74)	0.99	6.36 (-2.30–15.02)	0.15
2 h	-4.24 (-12.90–4.43)	0.34	-0.51 (-9.19–8.17)	0.91	9.74 (1.07–18.40)	0.03
4 h	-1.08 (-9.76–7.60)	0.81	-2.22 (-10.92–6.47)	0.61	2.33 (-6.36–11.03)	0.60
5 h	-3.22 (-11.89–5.44)	0.46	0.34 (-8.34–9.01)	0.94	-0.72 (-9.39–7.94)	0.87
8 h	-0.56 (-9.24–8.13)	0.90	-2.24 (-10.94–6.47)	0.61	3.17 (-5.52–11.86)	0.47
9 h	0.19 (-8.47–8.86)	0.97	-6.82 (-15.50–1.86)	0.12	4.61 (-4.05–13.27)	0.30



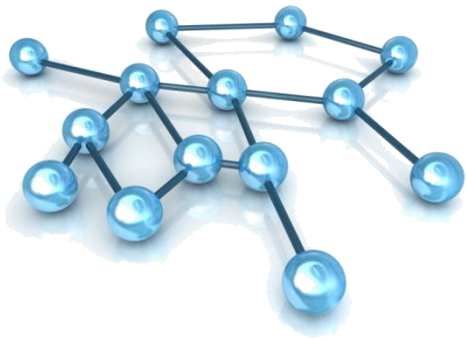
proarrhythmic potency assessment

in silico – in vitro – in vivo extrapolation

IN VITRO INFORMATION

Domperidone

- in vitro hERG inhibition – IC_{50} – $0.057 \mu\text{M}$ based on the HEK/room study – Claassen 2005
- no data regarding the IKs and other currents inhibition (*QSAR prediction?*)



proarrhythmic potency assessment

in silico – in vitro – in vivo extrapolation

ToxComp
system

Tox-Comp.net

file parameters help

ionic channels

drug concentration

cardiomyocytes

populations

settings

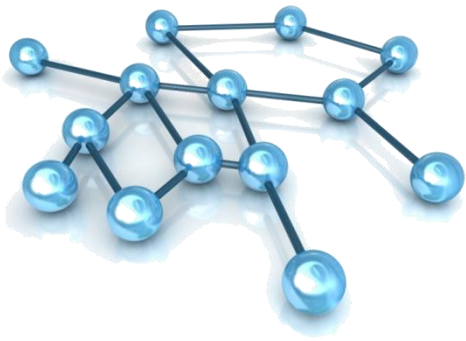
results

Tox-Comp.net

[2011.09.06 13:41:03]: ToxComp started

Start simulation

save log clear log



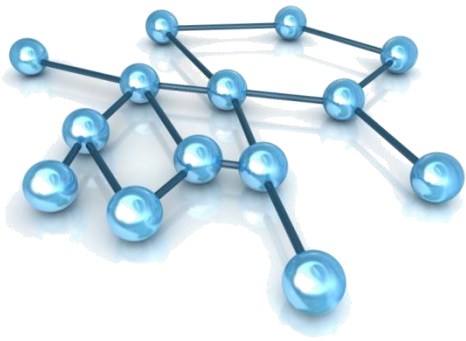
proarrhythmic potency assessment

in silico – in vitro – in vivo extrapolation

SIMULATION RESULTS

Domperidone in combination

	no drug	single DOMP		combination DOMP	
Drug-concentration-[μM]	0	0.038	0.055	0.16	0.21
QT	293.33	314.50	319.04	330.42	332.67
SD	15.43	16.44	16.73	17.46	17.74
ΔQT	0.00	21.17	25.71	37.08	39.33
SD	0.00	1.65	2.09	3.19	3.51
95% CI	0.00	0.66	0.84	1.28	1.40



proarrhythmic potency assessment

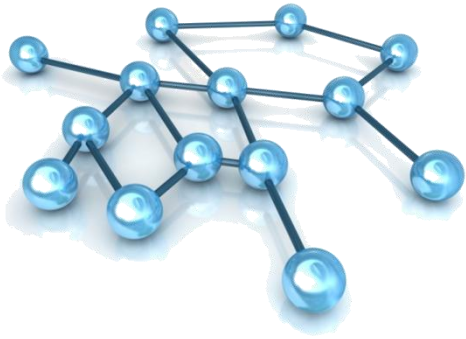
in silico – in vitro – in vivo extrapolation

August 24, 2011 — The antidepressant citalopram (Celexa, Forest Laboratories) should not be used in doses higher than 40 mg per day because of concerns that it can cause potentially fatal changes in heart rhythm, the US Food and Drug Administration warns.

Toxicology Observations

Citalopram Overdose: Late Presentation of Torsades De Pointes (TdP) With Cardiac Arrest

Asim F. Tarabar, MD^a, Robert S. Hoffman, MD^{a,b}, Lewis S. Nelson, MD^{b,c}

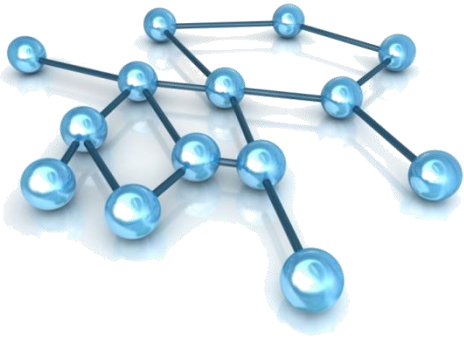


proarrhythmic potency assessment

in silico – in vitro – in vivo extrapolation

CLINICAL INFORMATION

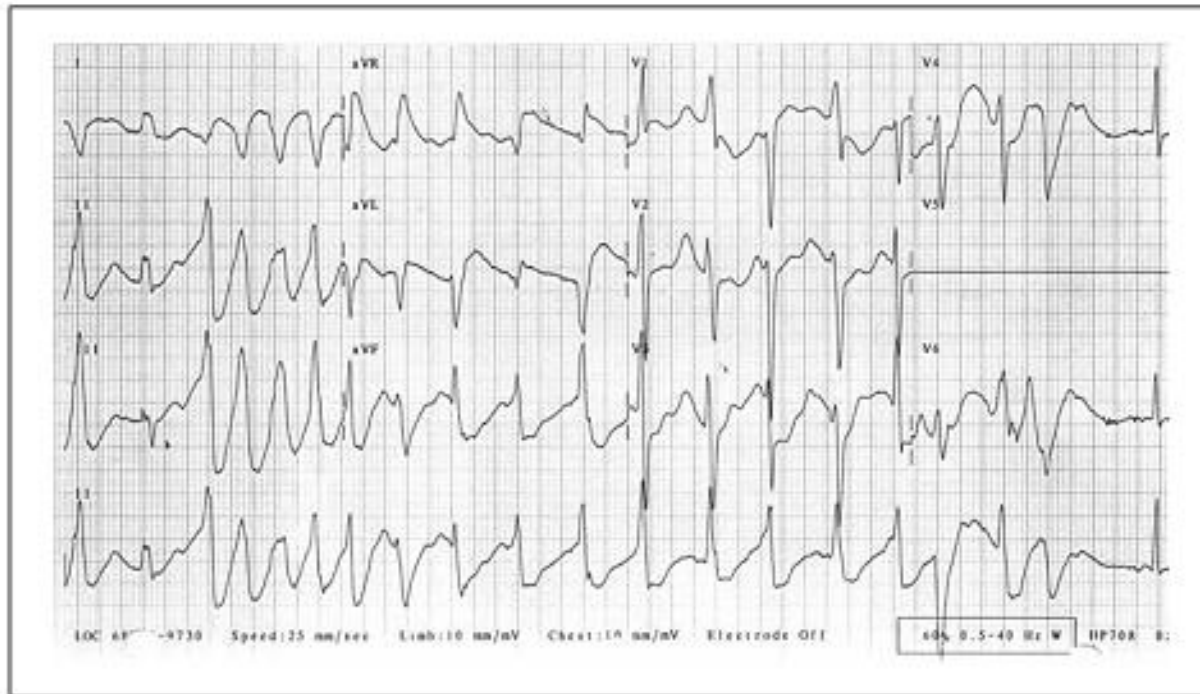
- 36 years old woman
- high dose of citalopram
- serum citalopram concentration (33 hours post-ingestion) was **477 ng/mL (1.47 μM)**; *therapeutic: 40–110 ng/mL (0.12 - 0.34 μM)*
- pulse, **102–150/minute**
- initial ECG showed sinus rhythm with a prolonged **corrected QT interval (572 msec)** with paroxysmal, self-limited runs of wide-complex tachycardia that appeared multifocal in nature

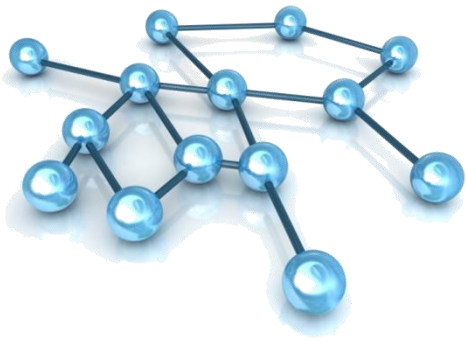


proarrhythmic potency assessment

in silico – in vitro – in vivo extrapolation

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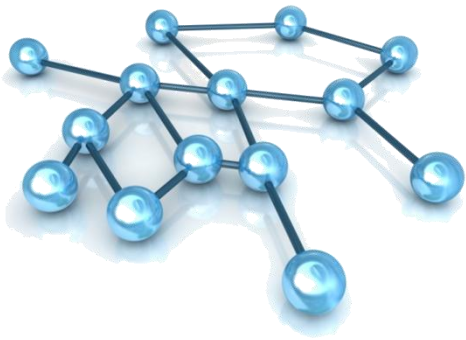
proarrhythmic potency assessment

in silico – in vitro – in vivo extrapolation

IN VITRO INFORMATION

Citalopram

- in vitro hERG inhibition – IC_{50} – 3.97 μ M based on the CHO/room study – Witchel 2002
- no data regarding the IKs and other currents inhibition (*QSAR prediction?*)



proarrhythmic potency assessment

in silico – in vitro – in vivo extrapolation

ToxComp
system

Tox-Comp.net

file parameters help

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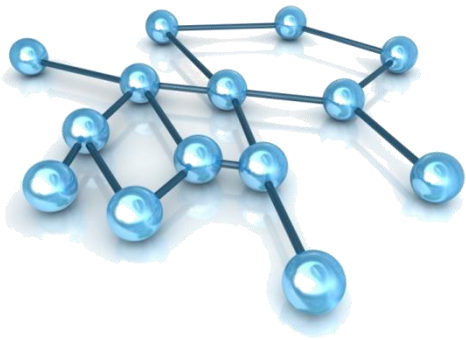
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proarrhythmic potency assessment

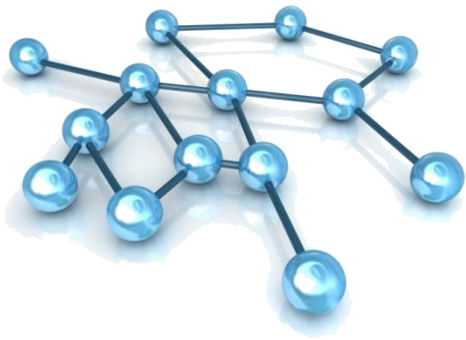
in silico – in vitro – in vivo extrapolation



RESULTS

Citalopram

- Drug-concentration-[μ M]:		0	0.34	1.47
- Ionic-currents-inhibition-[%]:	lkr:	0	0.16	0.46
	lks:	0	0.16	0.45



proarrhythmic potency assessment

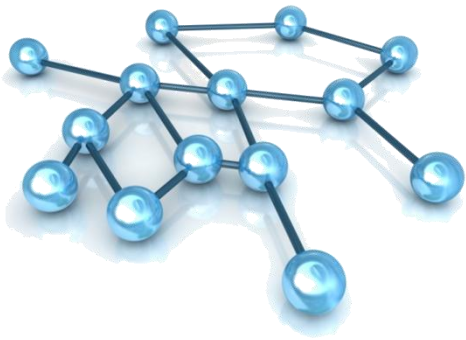
in silico – in vitro – in vivo extrapolation



RESULTS

Citalopram

- Drug-concentration-[μM]	0	0.34	1.47
QT[ms]	292	307	343
ΔQT -[ms]	0	15	51
	0%	5%	15%



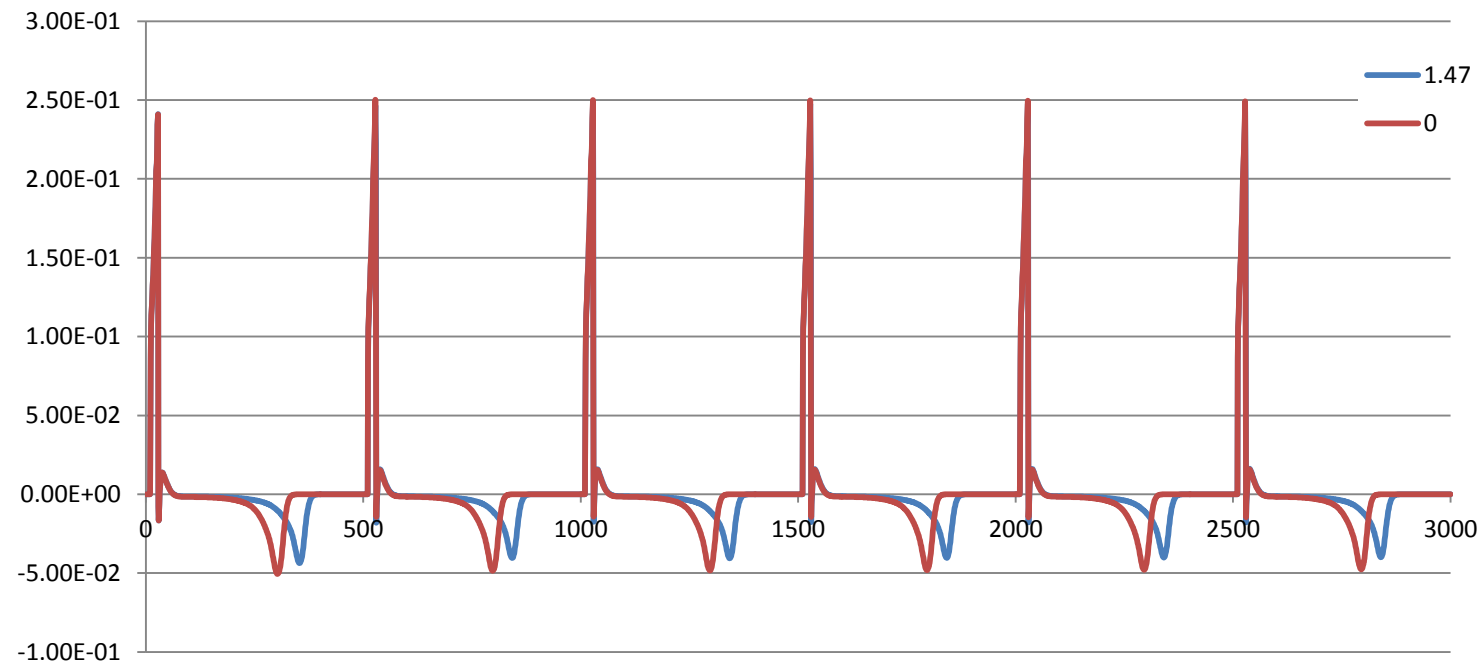
proarrhythmic potency assessment

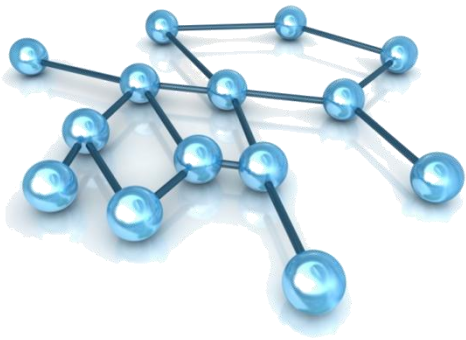
in silico – in vitro – in vivo extrapolation



RESULTS

Citalopram (120 beats/min)





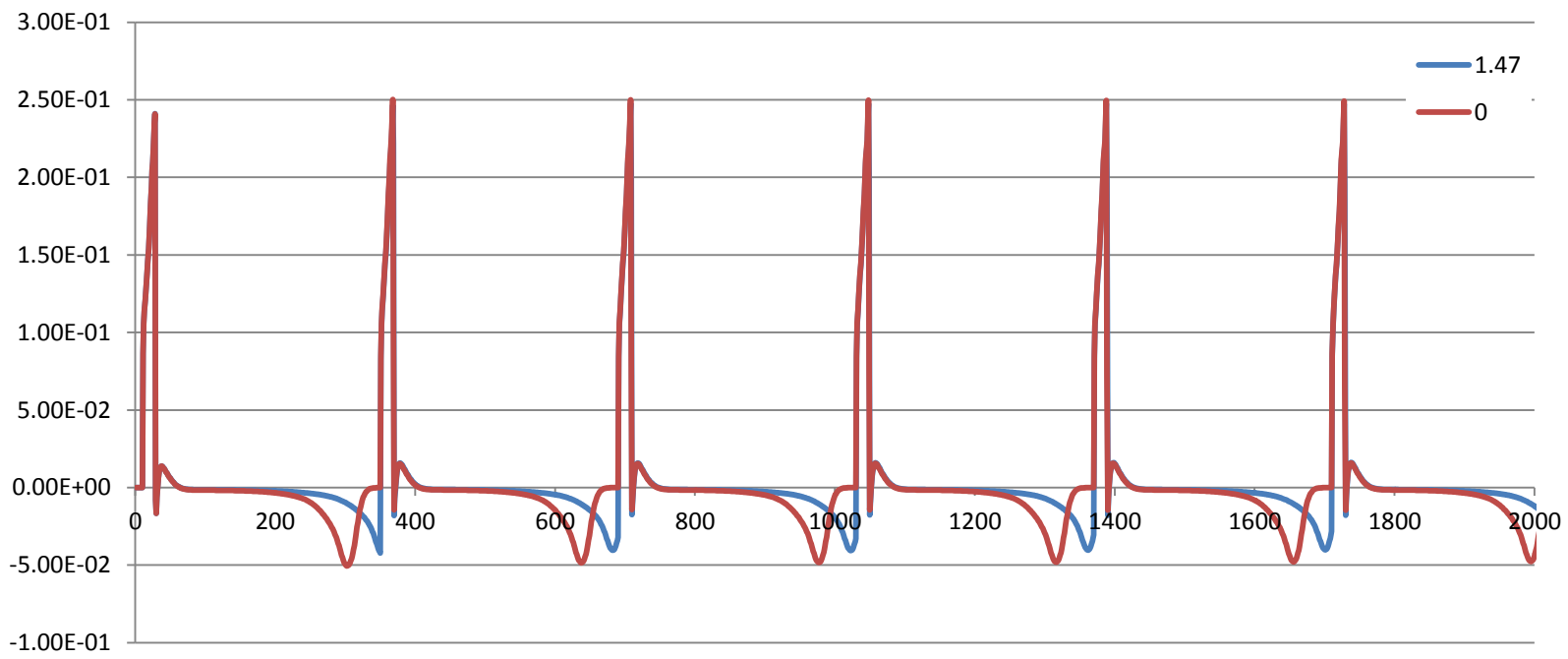
proarrhythmic potency assessment

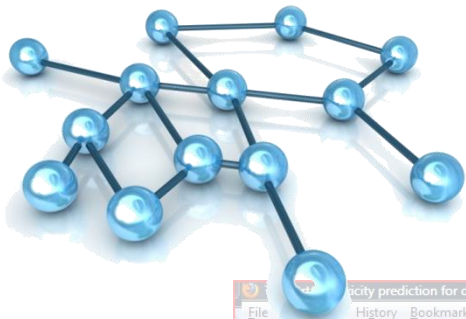
in silico – in vitro – in vivo extrapolation



RESULTS

Citalopram (150 beats/min)





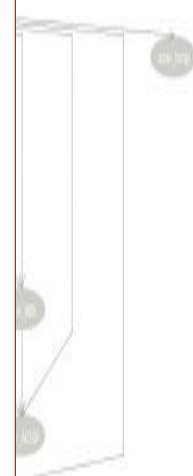
proarrhythmic potency *in silico*

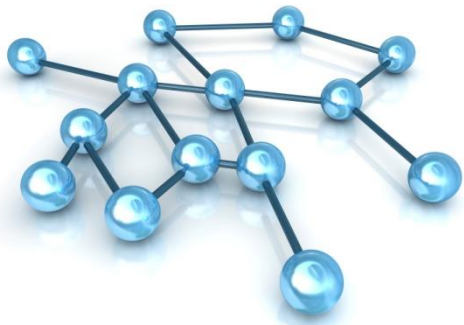
ToxComp.net

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more information can be found at the

www.tox-portal.net





acknowledgements

team

Barbara Wiśniowska PhD

Aleksander Mendyk PhD

Miłosz Polak

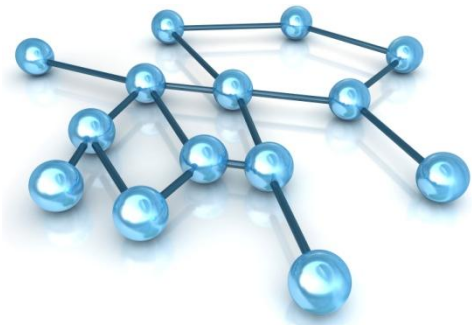
Kamil Fijorek

Anna Glinka

Małgorzata Kozłowska



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THANK YOU



Unit of Pharmacoepidemiology and
Pharmacoeconomics
Jagiellonian University Medical College

