Utility of preclinical PKPD modeling in QT safety testing

Sandra Visser & Piet van der Graaf

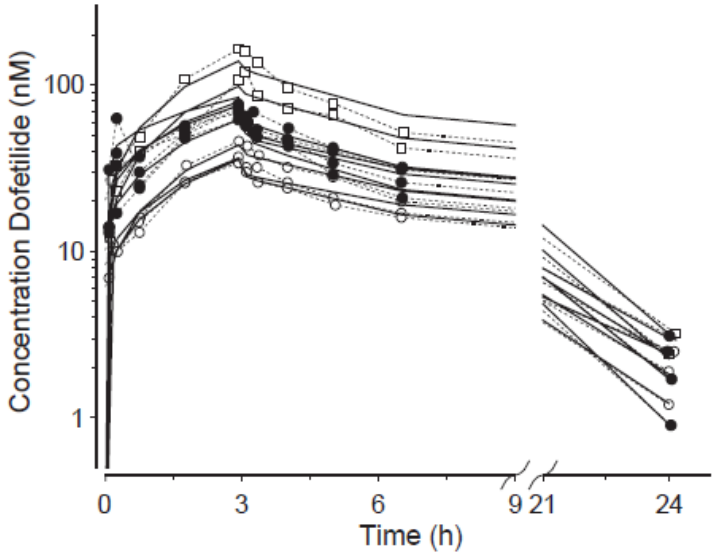
EMA/EFPIA M&S Workshop on the role and scope of modelling and simulation in drug development

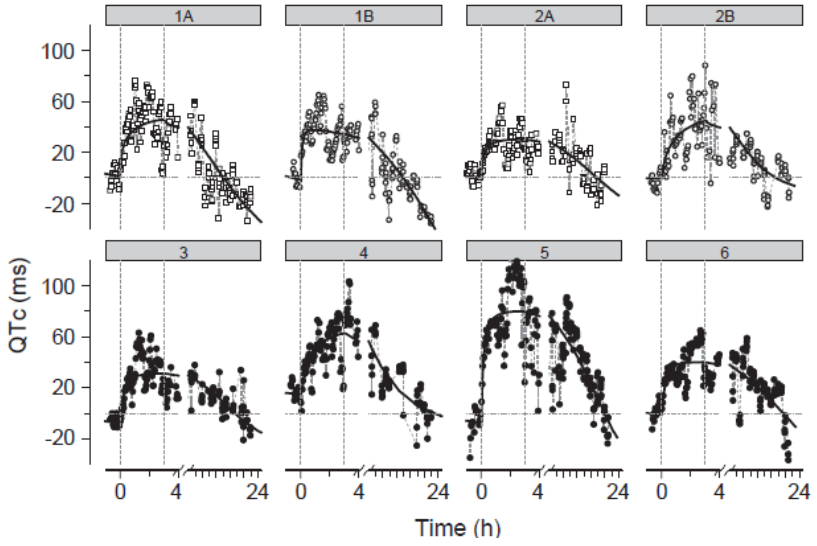
BOS1, London 1 December 2011

Introduction

- Following the development of ICH E14 there has been considerable attention to the power of clinical studies to detect drug effects on QTc
- However, there is no general agreement on the power of non-clinical studies to detect a given cardiovascular effect (BP, HR, QT etc) and this may contribute to concerns (raised a.o. by regulators) over the predictability of non-clinical studies
  - Divergent physiology and pharmacology
  - Definition of 'an effect'
  - What is the appropriate sensitivity to detect the desired effect
- Emerging approach is:
  - Define magnitude of effect that is a concern in humans
  - Define magnitude of effect in animals that predicts the effect in humans
  - Power the non-clinical studies to detect that magnitude of effect
- **Translation, study design and PKPD modeling are key to success**

Dofetilide in dogs: QT interval vs. Time





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Original article

Pharmacokinetic-pharmacodynamic modeling of drug-induced effect on the QT interval in conscious telemetered dogs

Anna Ollerstam [a,*], Sandra A.G. Visser [a], Anna H. Persson [a], Göran Eklund [a], Lars B. Nilsson [a], Tomas Forsberg [a], Stig Johan Wiklund [a], Johan Gabrielsson [b], Göran Duker [b], Ahmad Al-Saffar [a]

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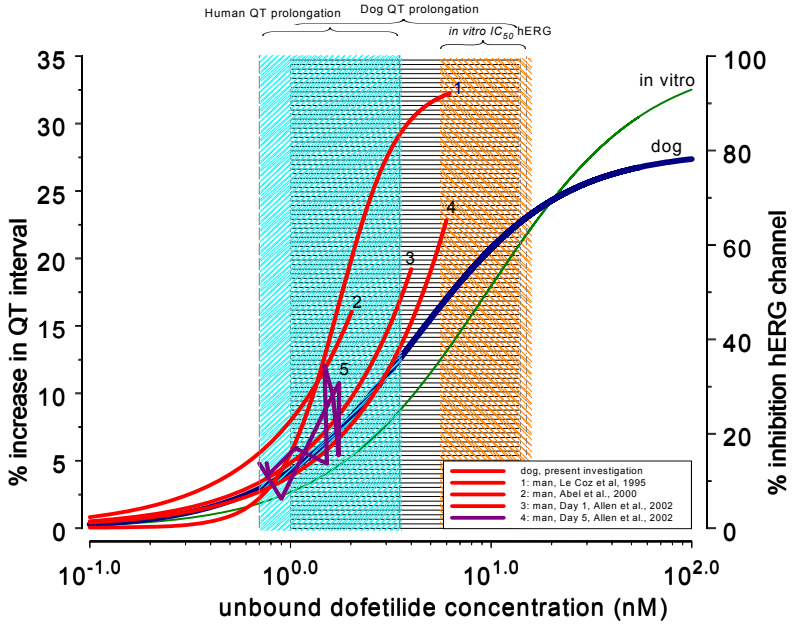


Cross-species translation of Dofetilide: role of baseline

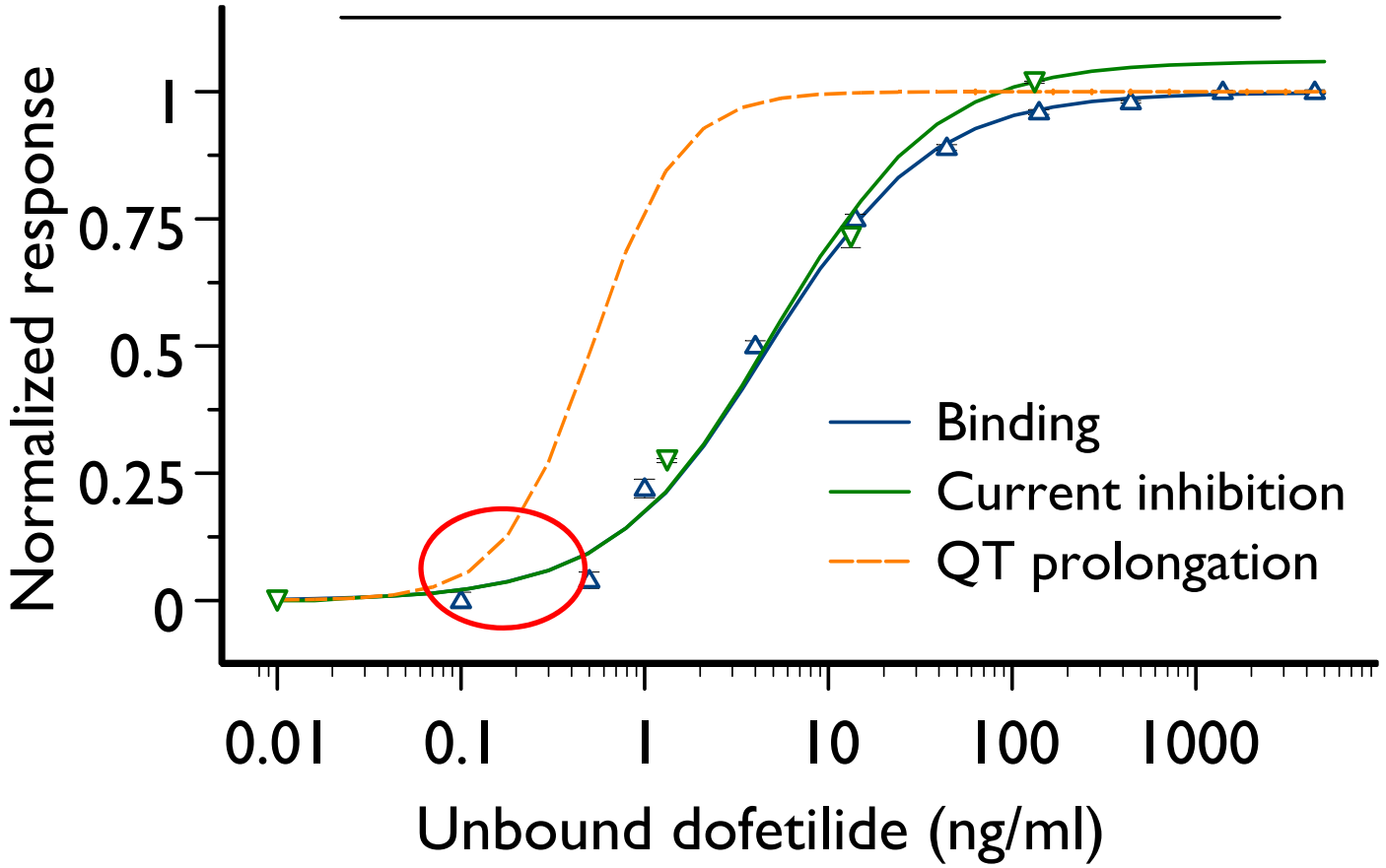
	Man[#]	Dog*	GP[&]
Baseline (ms)	386	212	148
E_{max} (ms)	105	59	41
% increase	27	28	28

10 msec in human = 5-6 msec in dog?
(i.e. 3% increase from BL)

[#]Jonker et al. 2005 *Ollerstam et al. 2006 [&]Pfizer internal

Dofetilide: apparent in vitro – in vivo potency mismatch

	In vitro hERG	QT in man
EC_{50} (ng/mL)	5.13 (rSE 15%)	0.98 (rSE 10%)

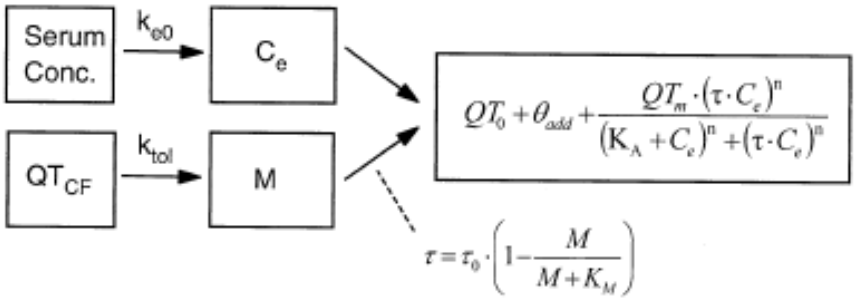


PK/PD Model for Dofetilide: operational model of QT prolongation

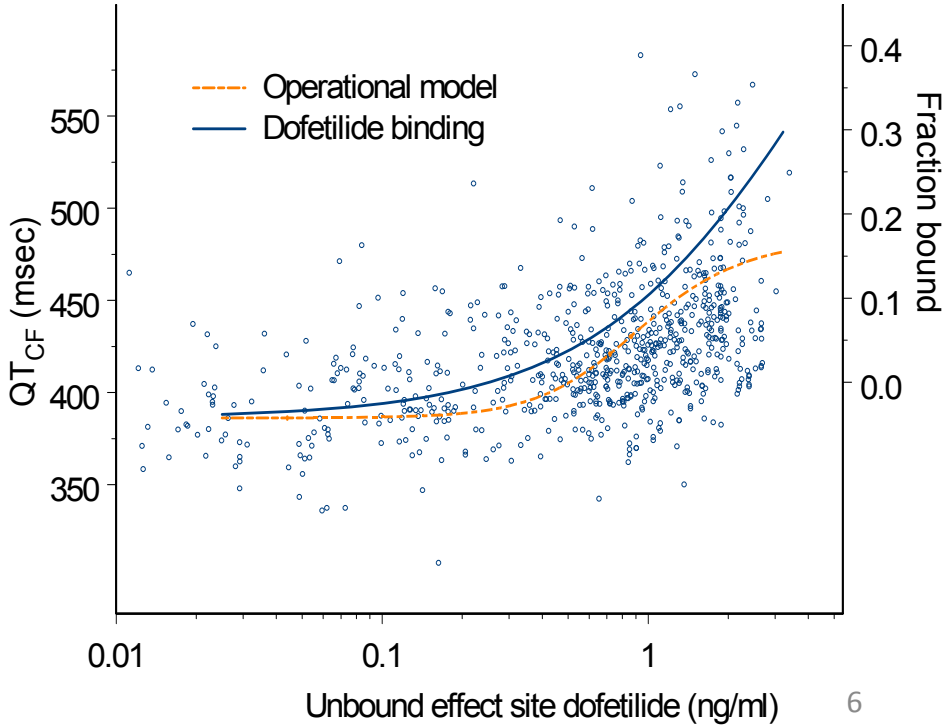
A pharmacokinetic-pharmacodynamic model for the quantitative prediction of dofetilide clinical QT prolongation from human ether-a-go-go–related gene current inhibition data

Daniël M. Jonker, PhD, Leslie A. Kenna, PhD, Derek Leishman, PhD, Rob Wallis, PhD, Peter A. Milligan, PhD, and E. Niclas Jonsson, PhD

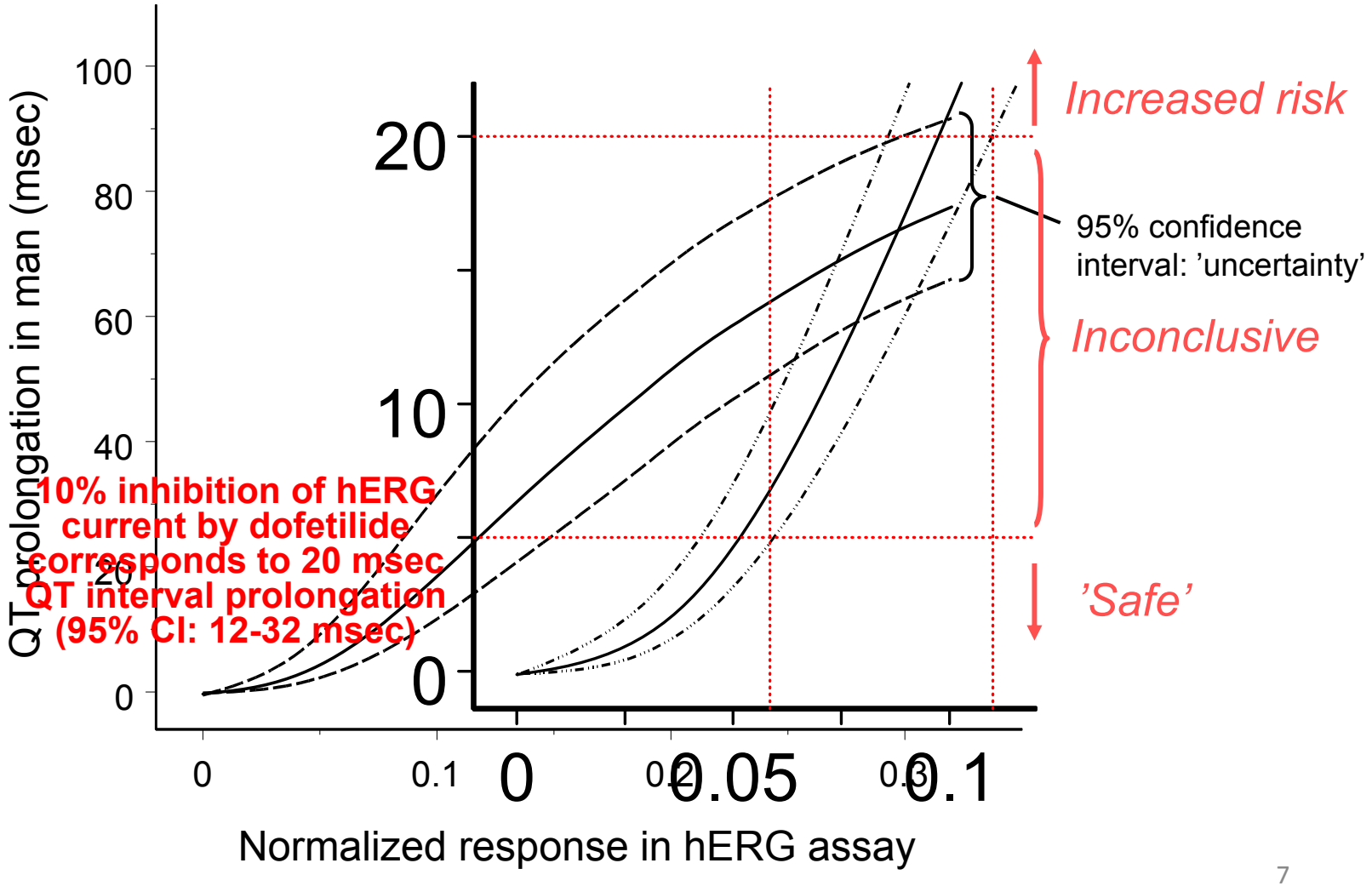
(Clin Pharmacol Ther 2005;77:572-82.)



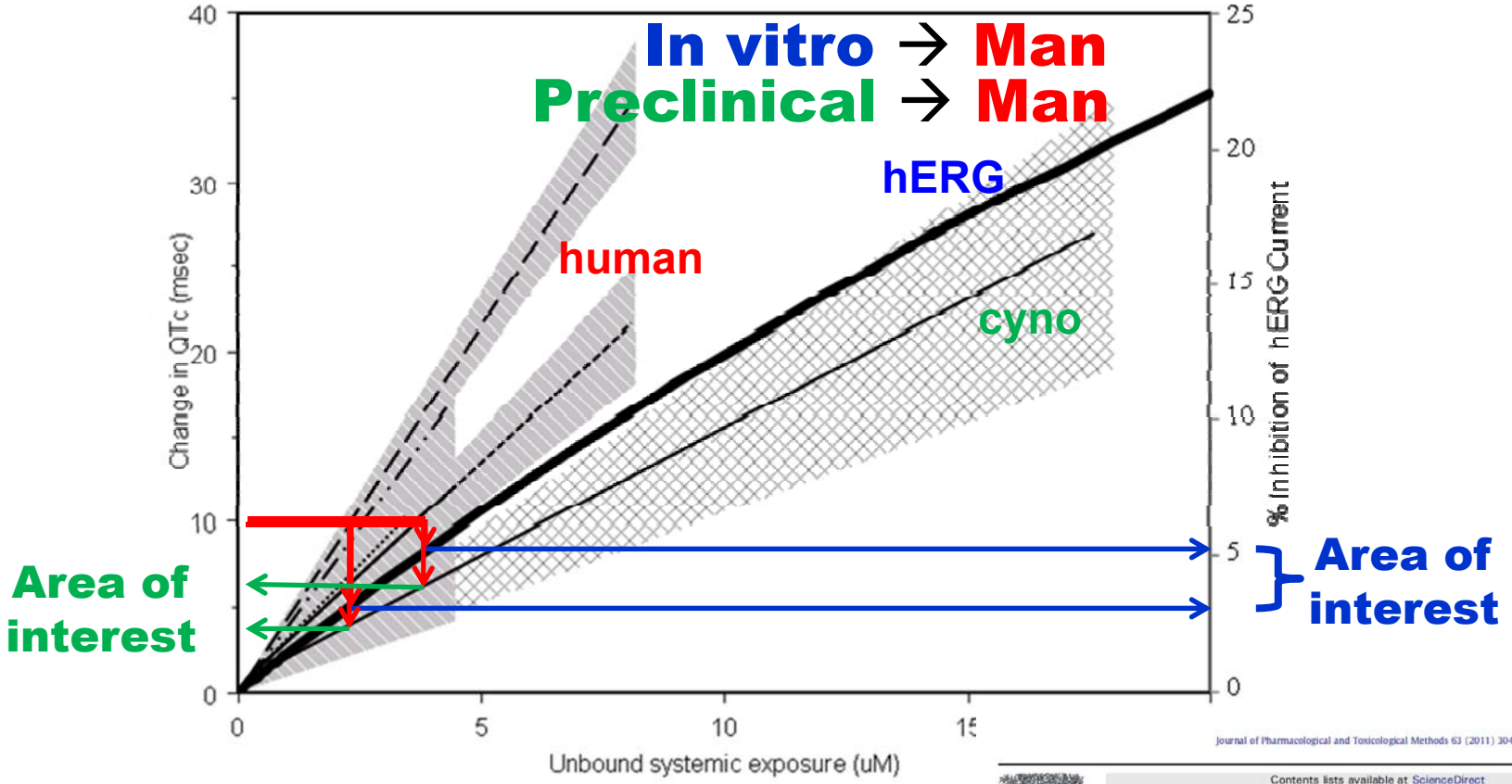
- Mechanistic PKPD modeling approach to deduce the translational link between in vitro and clinical

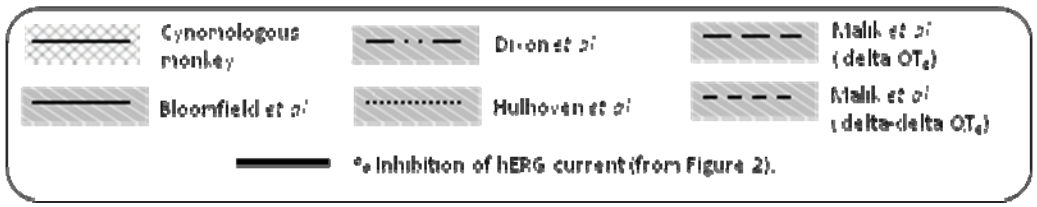


In vitro – in vivo Relationship: predicting QT risk



Moxifloxacin: Concentration-Effect Modelling as a Translational Tool





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Original article

Pharmacokinetic–pharmacodynamic modelling of the effect of Moxifloxacin on QT_c prolongation in telemetered cynomolgus monkeys

Kenny J. Watson [a], William P. Gorczyca [b], John Umland [c], Ying Zhang [c], Xian Chen [b], Sunny Z. Sun [b], Bernard Fermini [b], Mark Holbrook [d], Piet H. Van Der Graaf [a,e,*]

Consistent translation between in vitro and in vivo to dog

Pfizer Compound	hERG IC_{20} μM	Modelled [μM] for 10 msec change in dog	Fraction of hERG IC_{20}
A	6.9	2.3	0.33
B	0.57	0.29	0.51
C	2.04	0.63	0.31
D	1.6	0.4	0.23
E	16.7	7.6	0.45
F	2.5	2.2	0.9
Moxi	12.8	3.5	0.27

Prediction of the human QT safety profiles of new drug candidates

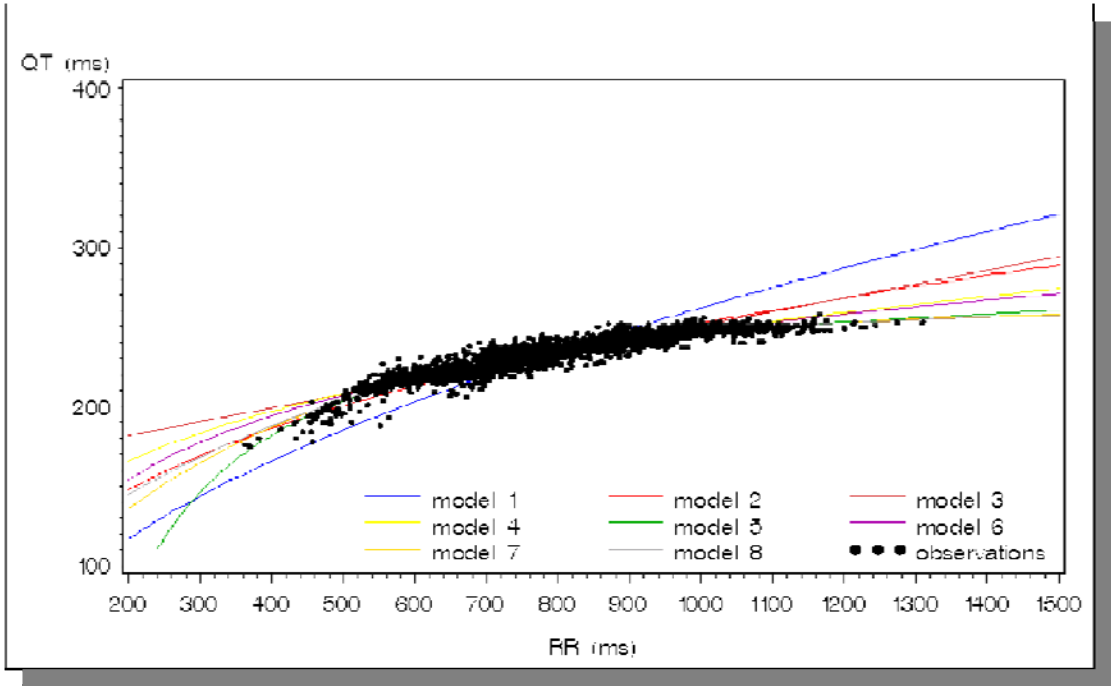
- ~5% hERG → ~5 msec dog/monkey → ~10 msec humans
  - Demonstrated for number of compounds (internal Pfizer) and between companies (AZ & Pfizer)
- Important issues to address
  - Experimental design to optimally and reliably detect small changes
    - hERG assay harmonization
    - PKPD design of in vivo dog studies
    - Clinical study design for QT assessement based on preclinical knowledge
  - Data analysis
    - QT correction (individual, baseline, vehicle, serial correlation)
    - Model-based analysis of hysteresis
  - Validation of human prediction
    - Retro- and pro-spective predictions
    - Build in vitro- vivo and clinical relationship for non selective hERG blockers

Experimental design

- Validate link between hERG protocol and in vivo results
  - Large differences in hERG protocols between companies
  - Build case for non-selective hERG blockers / multi channel screen

- In vivo study design based on PKPD principles
  - Gradual infusion of the compound and recording of washout phase at two or more dose levels.
  - Acclimatization of the dog to the experimental situation to reduce the influence of rapid changes in autonomic tone on the QT interval
  - Ex vivo assessment of plasma protein binding determination to facilitate the kinetic-dynamic analysis are considered essential for the estimation of the QT interval safety margin
  - PKPD modeling: allow a thorough kinetic-dynamic analysis in order to generate the true unbound concentration- response relationship at equilibrium accounting for hysteresis.
- Harmonization discussions
  - Best practice meetings Safety Pharmacology Society, Sept 2010
  - Pfizer interactions with FDA
  - Top Institute Pharma workpackage CV/Safety: recommendations by 2012

Example dog QT interval correction



1. Bazett
2. Friedricia
3. Van de Water
4. Individual exponent
5. Linear
6. Davies and Middleton
7. Raunig
8. Gompertz

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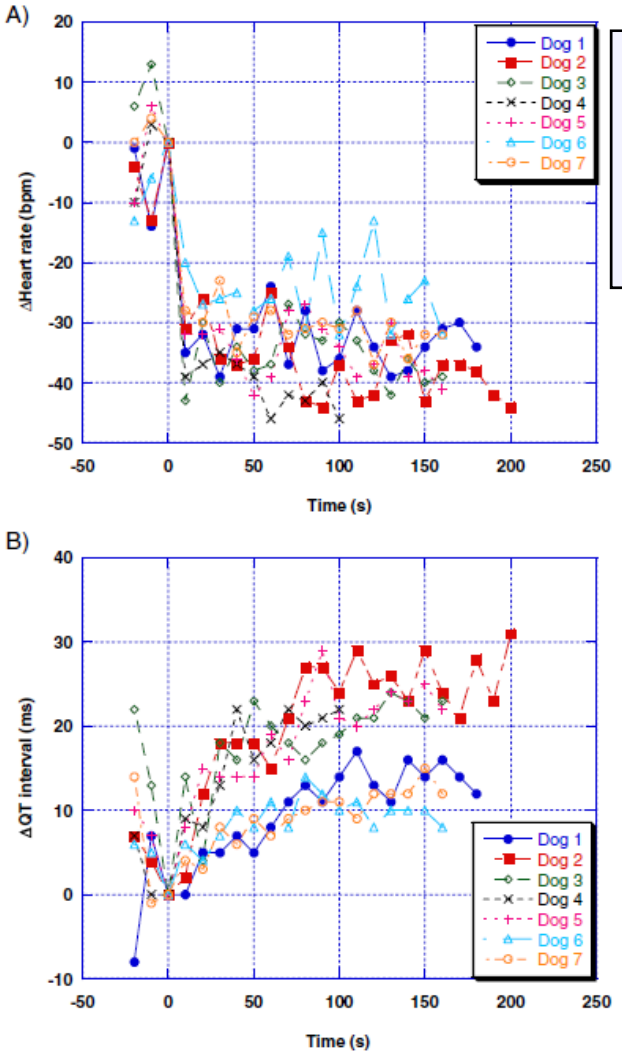
Original article

A novel approach to data processing of the QT interval response in the conscious telemetered beagle dog

Anna Ollerstam [a,*], Anna H. Persson [a], Sandra A.G. Visser [a], J. Magnus Fredriksson [a,1], Tomas Forsberg [a], Lars B. Nilsson [a], Göran Eklund [a], Stig Johan Wiklund [a], Johan Gabrielsson [b], Göran Duker [b], Ahmad Al-Saffar [a]

- QT interval-heart rate relationship and vehicle response were individual-specific and corrections should therefore be made individually using a linear model

Lag time in QT interval adaptation to an abrupt decrease in heart rate



	QT Emax (ms)	t1/2 (s)	QTss 75% (s)	QTss 90% (s)
Mean	**19**	**27**	**54**	**89**
se	2	5	9	15

QT interval data after abrupt changes in heart rate should be excluded from the analysis due to delay in the QT interval response

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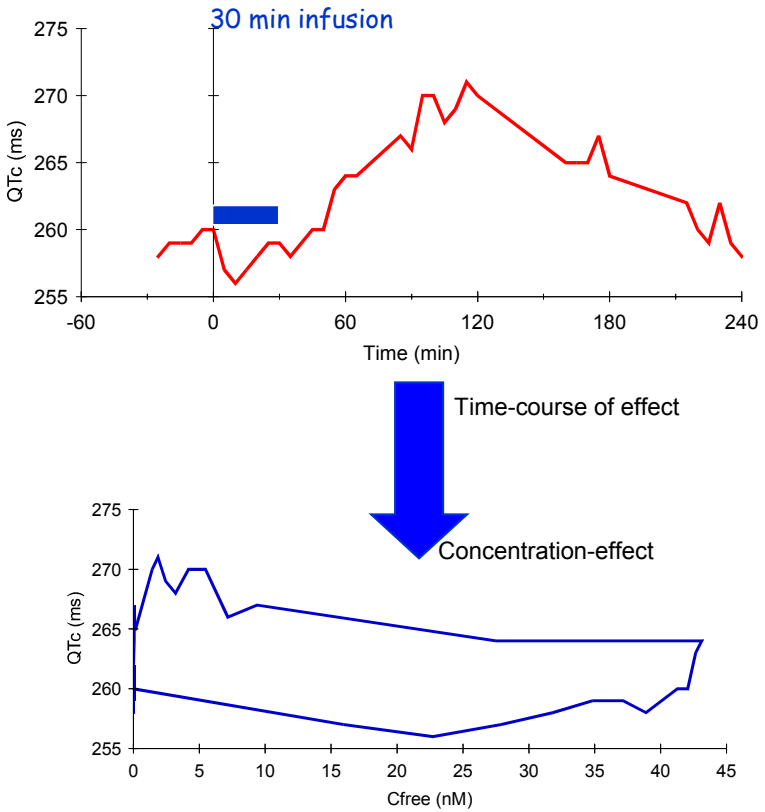
Hysteresis: Model Based Approach needed for correct assessment of QT

- **Very commonly observed in preclinical QT testing and also common for other CV endpoints: BP, HR, Contractility**
- Extend ranges from minutes to hours and can vary between compounds from same program
- Can provide important information about MOA and hence guide risk management strategy:
  - Direct or indirect effect
  - Target related or not
  - Metabolite
- Limited information available regarding translation to man
- **Ignoring hysteresis may lead to incorrect estimation of QT safety window**
- PKPD analysis of the individual concentration-effect relationship and confounding factors such as hysteresis provides a better prediction of the safety profiles of new drug candidates

QTc effect of PF-A in dog



Preclinical PKPD for CV Safety Testing: Value proposition

- **Application of PKPD principles and methods can increase effectiveness and efficiency of preclinical cardiovascular safety testing:**
  - **Increased confidence** in safety assessment and definition of safety margin through characterization of concentration-effect relationship
  - Support **mechanistic interpretation** of findings through better understanding time-course of effect
  - More **efficient** study design and data analysis can help to reduce use of animals (**3R**'s principles)
- **PKPD models provide common language for translational safety pharmacology between species:**
  - Utilise preclinical PKPD models to **guide human trial design**

Discussion

- (How) Can preclinical PKPD safety studies provide a basis for a risk management strategy that does not involve TQT?