Development and validation of a mechanism-based PK/PD model for the in vitro-in vivo prediction of QT prolongation by dofetilide

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Introduction

Drug-induced QT prolongation is an important biomarker for the risk of heart arrhythmias. Blockade of hERG currents is frequently used as an *in vitro* marker for this risk, but the relationship between hERG blockade and QT prolongation has not been determined in a quantitative manner.

The aim of the present work was to establish an integrated PK/PD model relating the action of the selective I_{KR} inhibitor dofetilide at the hERG potassium channel *in vitro* to its QT prolonging effects in man.

Methods

A joint analysis was performed to determine the affinity and activity of dofetilide in recombinant cell cultures and its QT effects in 5 clinical studies. These studies included 80 healthy volunteers and 17 patients with ischaemic heart disease and are summarized in Table 1.

The population analysis was performed in NONMEM in two steps. In the first step, the PK model was developed and covariates were identified in a semi-automated fashion. In the second step, the individually estimated dofetilide concentrations were used to drive the PD model. By including the *in vitro* dofetilide affinity in the operational model of pharmacological agonism[1] (Figure 1B), an estimate was obtained for the efficiency of the transduction from ion channel binding into the QT effect.

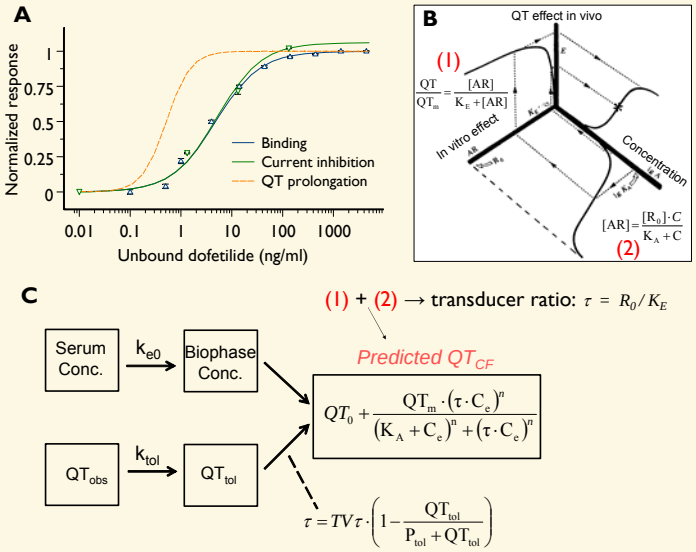

*Figure 1. The discrepancy between in vitro and in vivo observations (**A**) was modeled by using the operational model of pharmacological agonism (**B**). The PD model contained an effect compartment and a tolerance compartment (**C**).*

	A		B	C	D	E
Design	Dose escalation		Cross-over (5 days)	Cross-over	Dose escal.	Parallel (24 days)
Doses	4, IV		10/15, PO	1, IV/ PO	6, PO	47, PO
Serum sampl.	22 (13-26)		3 (0-22)	12	11	10 (0-15)
QT obs.	24		6/5	9	11	(205)
Isch.Heart Dis.	+	-	-	-	-	-
Subjects	17	8	25	9	12	26
Median age (years)	57 (42-69)	61 (44-70)	25 (18-41)	22 (18-30)	23 (19-45)	24 (19-35)
Median body weight (kg)	82 (60-95)	65 (47-91)	69 (57-80)	65 (56-75)	75 (57-90)	75 (62-84)
Median CL_{CR}	87 (43-128)	63 (41-103)	92 (72-120)	96 (70-140)	102 (77-140)	103 (72-119)

Table 1. Summary of clinical study characteristics.

Results

A 3-compartment PK model with first-order absorption after oral administration and a lag time characterized the time course of dofetilide concentrations well. Three covariate relations were identified by using stepwise forward selection followed by backward elimination within NONMEM[2] (Figure 2 and Table 2).

Fridericia-corrected QT observations were adequately described with the operational model including an effect compartment (Figure 3 and Table 3). Based on the *in vitro* affinity of 4.79 ng/ml, the estimate of τ indicated the presence of a modest ion channel reserve. The development of tolerance upon chronic administration was best described by a decrease of τ driven by the QT effect (Figure 1C).

Case deletion diagnostics did not indicate any structural between-study differences for the PK and PD parameters, except for those parameters that were supported by a single study only (Figure 4).

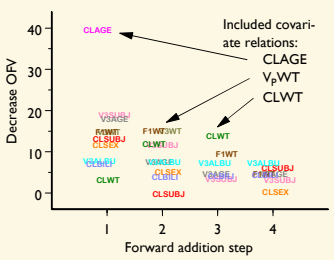

Figure 2. Covariate selection for the PK model parameters.

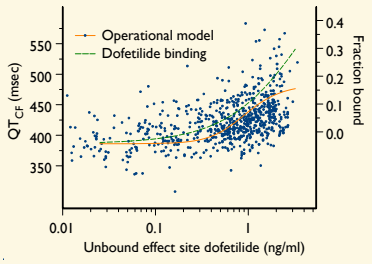

Figure 3. Extrapolation of in vitro potency versus the operational model estimates

	Est.	rel S.E.	CV	rel S.E.	Covariates
CL (L/h)	17.9	.04	13%	.32	CLAGE (L/h/year)
V_C (L)	14.8	.16	46%	.50	-0.0068 .19
k_A (/h)	0.89	.12	23%	.76	VPWT (L/kg)
t_{lag} (h)	0.43	.024			0.0072 .43
Q_1 (L/h)	505	.27	107%	.46	CLWT (L/h/kg)
V_{P1} (L)	134	.039	18%	.33	0.0060 .46
Q_2 (L/h)	8.31	.23	-		
V_{P2} (L)	63.7	.13	-		
F	0.88	.037	11%	.52	
Add ε (ng/ml)	0.028	.25	-		
Prop ε ( )	0.22	.059	-		

Table 2. PK parameter estimates.

	Est.	rel S.E.	CV	rel S.E.
QT_m (msec)	108	.52	70%	.58
τ ( )	5.8	.44	43%	.54
n_H ( )	2.28	.15	-	
k_{e0} (/h)	3.45	.04	-	
k_{tol} (/h)	.0061	.14	-	
P_{tol} (msec)	130	.26	-	
Add ε (msec)	15.2	.03	-	
Corr (τ, QT_m)	-0.92	.6	-	
Covariate: τQT_0	0.00592	.16	-	

Table 3. PD parameter estimates.

Conclusions

The quantitative relationship from the hERG assay to man was established using a selective I_{KR}-inhibitor. This PK/PD model scaled activity in the hERG model more accurately compared to extrapolation of dofetilide potency in the hERG assay. QT effects were adequately described for varying doses and administration routes and in both patients and healthy volunteers, demonstrating the general applicability of the proposed model.

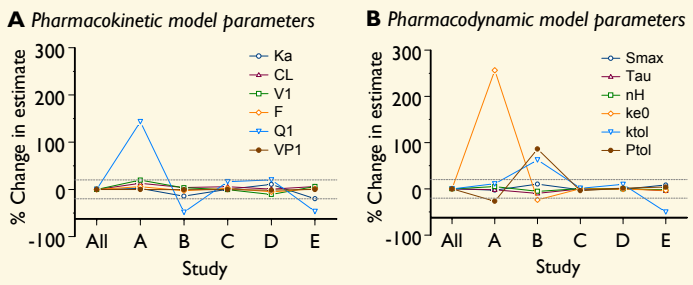

Figure 4. Case deletion diagnostics by study exclusion.

References: 1. Black, J, Leff, P. Operational models of pharmacological agonism. *Proc.R.Soc.Lond.B.* 1983; **220**:141-162.
2. Jonsson, EN, Karlsson, MO. Automated covariate model building within NONMEM. *Pharm Res* 1998; **15**: 1463-1468