Warfarin PKPD – Theory, Body Composition and Genotype

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Objectives

1) **Apply a theory based mechanistic model to describe the pharmacokinetics and pharmacodynamics S- and R-warfarin [1]**
2) **To explore the effect of body size [2], body composition [3] and genotype on warfarin PKPD parameters.**

Methods

Blood samples for S- and R-warfarin concentrations were taken in addition to measurement of International Normalized Ratio (INR) as part of clinical care of 264 patients (44% female; 6% CYP2C9 *1/*3; 17% VKORC1 GA/GG; 44% CYP4F2 CT/TT).

Size metrics

- Total body weight (TBW)
- Fat free mass (FFM) [2]
- Normal fat mass (NFM) [3]
  - NFM=FFM+Ffat*(TBW-FFM)
  - Ffat is a drug specific parameter that quantifies the relative contribution of fat to allometric size relative to FFM
  - Ffat was estimated separately for size related parameters

Pharmacokinetic model

Total (bound plus unbound) concentrations were measured by UPLC/MS-MS. Genotypes were measured using pyrosequencing of DNA extracted from blood leukocytes. Oral bioavailability assumed to be 1.

***In Vitro* Prothrombin Complex Activity (PCA) and INR**

Plasma from 25 healthy subjects and 25 patients was diluted and INR measured. The INR was predicted from PCA using a 2 parameter model [4].

$$INR = A/PCA + B$$

Simple dilution theory predicts A=1 and B=0.

Pharmacodynamic and Turnover model

The PKPD model assumed an immediate effect on the turnover of prothrombin complex activity (PCA). INR was predicted from PCA. A sequential population PK parameter with data method was used to estimate PD and turnover parameters.

Estimation and model selection

- Data were analyzed using NONMEM 7.3.0 (ADVAN13 NSIG=3, SIGL=9, TOL=9).
- Between subject variability and between occasion variability were estimated for all PK parameters. RUV is residual unidentified variability.
- Model selection was based on changes in objective function value (OFV).

Model evaluation

- Model evaluation was based on parameter plausibility and prediction-corrected visual predictive checks (VPC).

Table 1 Age and Size Metrics for the Patient Population

Statistic	AGE y	TBW kg	HT cm	BMI kg/m²	FFM kg	FAT kg
Median	55.5	61	165	22.8	46.5	16.2
2.5%	24.6	40	150	16.5	29.7	6.0
97.5%	75.4	86	180	29.7	63.3	29.2

Table 2 PK bootstrap parameters

Parameters	Average	2.5%	97.5%	RSE
CL-S L/h/70kg	0.234	0.197	0.272	11%
V-S L/70kg	25.40	22.40	28.41	6%
CL-R L/h/70kg	0.141	0.120	0.155	12%
V-R L/h	16.99	15.04	18.90	6%
FCYP2C9 *1/*3 CL-S	0.818	0.652	0.975	11%
FCYP2C9 *1/*3 CL-R	1.220	1.025	1.401	8%
RUV-S prop	0.263	0.247	0.277	3%
RUV-S add mg/L	0.005	0.002	0.008	27%
RUV-R prop	0.230	0.217	0.241	3%
RUV-R add mcg/L	0.000	0.000	0.000	0%

Table 3 In Vitro PCA-INR bootstrap parameters

Parameters	Average	2.5%	97.5%	RSE
A healthy	0.482	0.452	0.508	3%
B healthy	0.409	0.365	0.449	5%
A patient	0.560	0.526	0.592	3%
B patient	0.386	0.340	0.432	7%

Table 4 PKPD and turnover bootstrap parameters

Parameters	Average	2.5%	97.5%	RSE
C50-S mg/L	0.386	0.261	0.552	21%
HILL	2.53	2.08	3.04	10%
T2PCA h	12.2	11.0	13.6	6%
IC50-R mg/L	21.8	0.92	198	257%
FVKORC1 AA C50	0.719	0.605	0.806	7%
FCYP4F2 CC C50	0.767	0.637	0.869	8%
FCYP4F2 CT C50	0.761	0.649	0.881	8%
RUV prop	0.180	0.168	0.191	3%

PKPD Structural Model with Feedback

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$DES
   CS=A(2)/VS ; S-warfarin concentration
   CR=A(3)/VR ; R-warfarin concentration
   PCA=A(4)   ; Prothrombin Complex Activity
   C50I=C50*(1+CR/RIC50); Antagonist effect of R- on S-warfarin
   PD = EMAX/(1+(CS/C50I)**(-HILL)) ; More efficient Smax model
   RATEIN = KA * A(1) ; Racemic warfarin input rate
   DADT(1)= -RATEIN
   DADT(2)= 0.5*RATEIN - CLS*CS ; S-warfarin PK
   DADT(3)= 0.5*RATEIN - CLR*CR ; R-warfarin PK
   DADT(4)= RPCA*(1 - PD) - KPCA*PCA ; PCA turnover
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Results

- The warfarin PK model had first-order input, one compartment distribution and first-order elimination. The input was assumed to be the same for both enantiomers with enantiomer specific estimates for CL and V. Theory based allometry and fat free mass described size associated differences. There were no differences associated with sex after accounting for size. CYP2C9 (rs1057910, A>C) *1/*3 genotype had CL reduced for S- compared with *1/*1, but increased for R-warfarin. Bootstrap statistics for CL-S and V-S for each enantiomer and genotype effects on CL-S and CL-R are shown in Table 2 and VPC in Figure 1.
- The *in vitro* parameters for the relationship between PCA and INR were markedly different (A=0.560, B=0.386) from theory based values (A=1, B=0). There was a small difference between plasma from healthy subjects and patients. Bootstrap estimates are shown in Table 3.
- A sigmoid Emax pharmacodynamic model inhibiting PCA synthesis as a function of S-warfarin concentration predicted INR. The theory based model fit for INR was similar to the empirical model. R-warfarin effects were small and better described by competitive antagonism of S-warfarin inhibition than by direct inhibition. VKORC1 (rs9923231,-1639G>A) AA and CYP4F2 (rs2108622,C>T) CC or CT genotype had lower C50 for S-warfarin. Bootstrap statistics for the potency of S-warfarin (C50-S) and R-warfarin (IC50-R), the turnover half-life of PCA (T2PCA) and the genotype effects on C50-S are shown in Table 4 and VPC in Figure 2.

Figure 1 Pred Corrected VPC S- and R-warfarin concentrations

Observed (black), Predicted (red) 5, 50, 95 %iles, with Predicted 95% Confidence Intervals (gray)

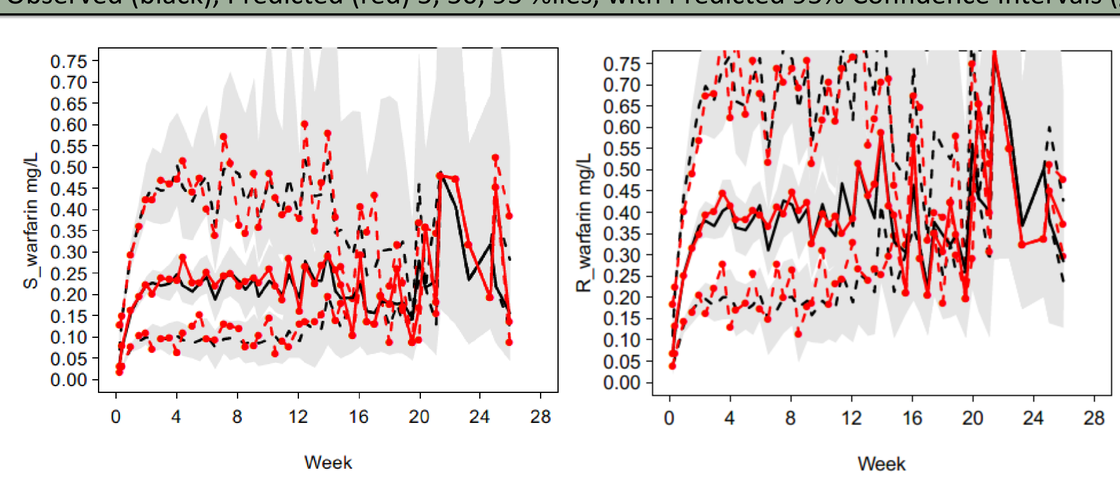
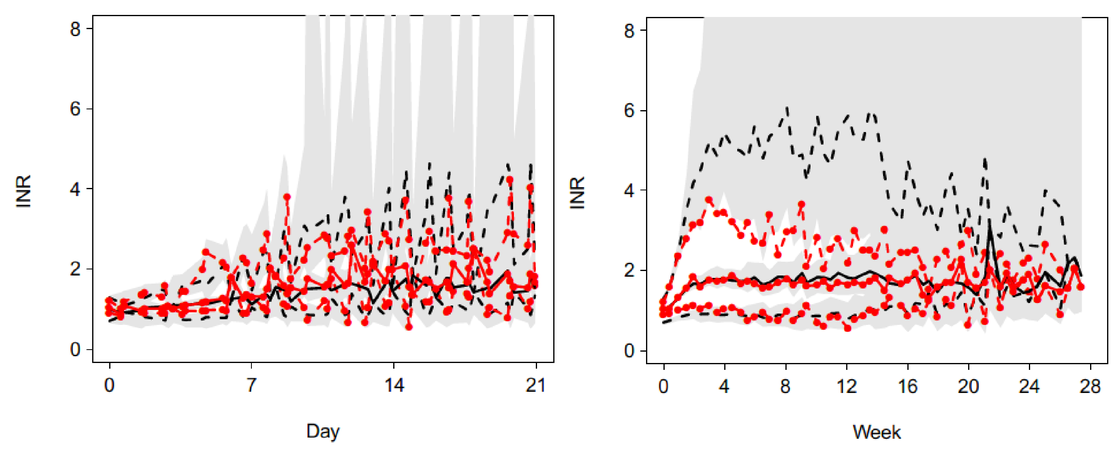


Figure 2 Pred Corrected VPC International Normalized Ratio



Conclusions

- **A theory based PKPD model describes warfarin concentrations and clinical response.**
- **Expected PK and PD genotype effects were confirmed. CYP2C9 mutation is associated with an increase in R-warfarin clearance.**
- **The role of theory based allometric scaling of PK parameters using fat free mass was identified.**
- **The *in vivo* relationship between PCA and INR was consistent with a simple inverse relationship as expected from theory. The *in vitro* relationship was inconsistent with the theoretical relationship.**
- **R-warfarin behaves more like a competitive antagonist of S-warfarin than a less potent inhibitor of PCA synthesis.**

References

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