Prediction of warfarin exposure and INR response in children

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Conclusion

❖Allometricly scaled PK and KPD models developed from adult warfarin data appear to be useful as a basis for further development of more individualised warfarin therapy in children.

Background

Challenges in warfarin therapy

- Narrow therapeutic range
- Large variability in dose, ranging from < 1 to > 20 mg/day in adult patients

Predictors of dose variability in adults

- CYP2C9 (PK) and VKORC1 (PD) genotype
- Age, body size, diet, interacting drugs, target INR

Clinical situation for children

- Paucity of data
- 0.1-0.2 mg/kg common starting dose

Objective

Assess whether allometric weight scaling of published warfarin models [1] can predict exposure and INR response in a Japanese paediatric population [2].

Materials and Methods

- Paediatric study population described in Table 1.
- Children were genotyped for CYP2C9, but not VKORC1. All assigned VKORC1 A/A, the dominant genotype (>80%) in Asians.
- A schematic picture of the allometricly scaled KPD model is depicted in Figure 1.
- Prediction corrected VPCs [3] to evaluate model performance in children.

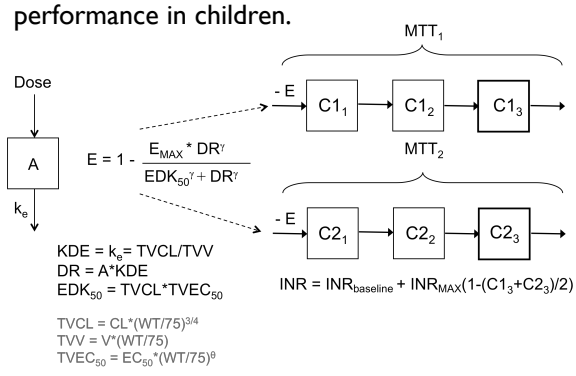

Figure 1. A schematic picture of the allometricly scaled KPD model

Table 1 Demographics and treatment details for children included in a Japanese warfarin study (PK data N=51, PD data N=49)

Sex, male/female	35/16
Weight	9.6 - 68.0 kg
Age	1 - 18 years
CYP2C9 genotype	*1/*1 n=45
	*1/*3 n=6
Stable daily warfarin dose	0.25 - 2.00 mg
	0.009 - 0.074 mg/kg
S-warfarin concentration (1 sample/subject)	7.9 - 478.3 ng/ml
Stable INR (1 sample/subject)	1.27 - 4.75

Results and Discussion

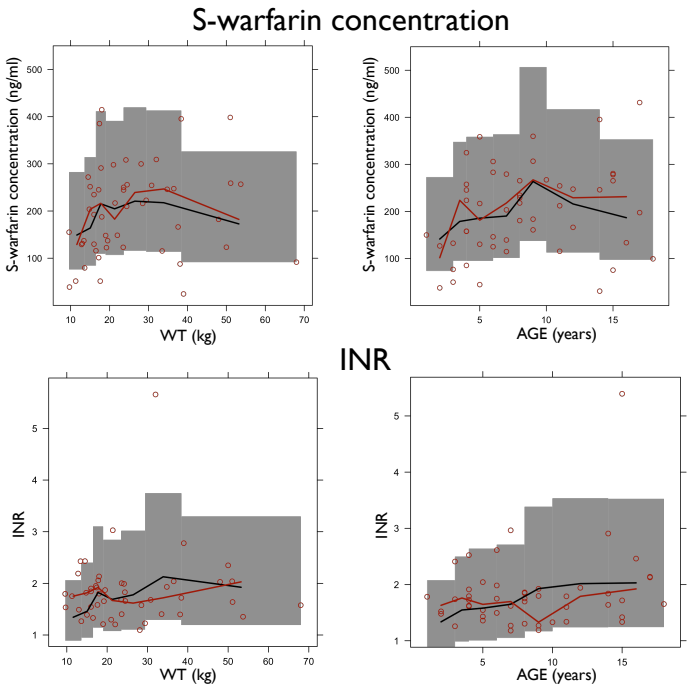

Figure 2. Prediction corrected VPCs of S-warfarin exposure (top) and INR response (bottom), with body weight (left panel) or age (right panel) as independent variable. Observations are presented as red circles, with medians as solid red lines. Model predictions are presented as 90% prediction intervals in gray, with medians as solid black lines.

- Good agreement between model predicted and observed warfarin exposure and INR response in children.
- Study sample small and limited to stable phase of therapy, with important covariate information partly missing.
- Analyses of data from a larger and more diverse paediatric population, with observations from all phases of therapy, will improve robustness of dose predictions in children.

References

[1] A-K Hamberg *et al. Clin Pharmacol Ther.* 2010; 87, [2] H Takahashi *et al. Clin Pharmacol Ther.* 2000; 68,[3] M Bergstrand *et al. AAPS J.* 2011; 13

Simulations give further support for the warfarin KPD model in children

Background VKORC1 and warfarin

- Warfarin - inhibitor of VKORC1 (Vitamin K epoxide reductase complex subunit 1), rate limiting enzyme in the Vitamin K cycle (Fig. 3).
- Single nucleotide polymorphism (SNP) in the *VKORC1* gene (-1639G>A) - predictor for warfarin dose.
- Three genotypes (G/G, A/G and A/A) with large ethnic differences in prevalence.
- The A allele associated with lower warfarin dose.
- Japanese paediatric study performed 2000, before *VKORC1* gene was identified (2004).

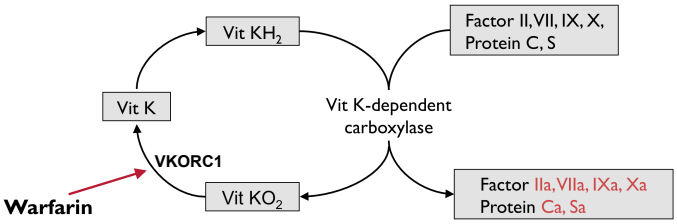

Figure 3. The Vitamin K cycle and VKORC1 - the polymorphic target enzyme for warfarin (a=activated form)

Objectives

- To compare model predicted VKORC1 genotype frequencies in the Japanese paediatric study population with expected genotype frequencies in an Asian patient population
- To compare model predicted and observed doses given model predicted VKORC1 genotype

Methods and Results

1. Simulate 1000 patients per subject and VKORC1 genotype given the expected joint IIV distribution and the allometricly scaled KPD model
2. Estimate dose distributions per genotype given observed INR (Fig. 4)
3. Assign each child most probable genotype (Fig. 4)
4. Compare model predicted and expected VKORC1 genotype distribution (Table 2)
5. Compare model predicted and observed doses (Fig. 5)

Table 2 Predicted and expected VKORC1 genotype frequencies

VKORC1	Model predicted frequency	Expected frequency*
G/G	8% (4)	2%
A/G	18% (9)	18%
A/A	74% (36)	80%

Fisher´s exact test: p=0.482 *IWPC unpublished data N=1648

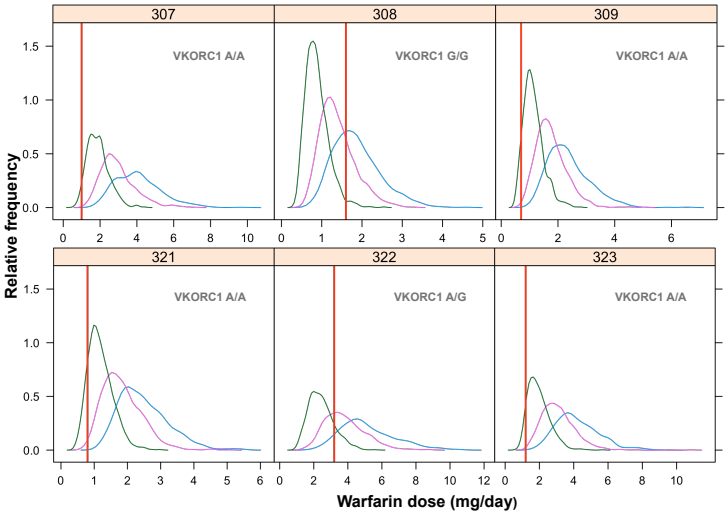

Figure 4. Examples of model predicted dose distributions per VKORC1 genotype (VKORC1 A/A, VKORC1 A/G and VKORC1 G/G), observed warfarin dose (I) and assigned (statistically most probable) VKORC1 genotype for 6 of the 49 Japanese children.

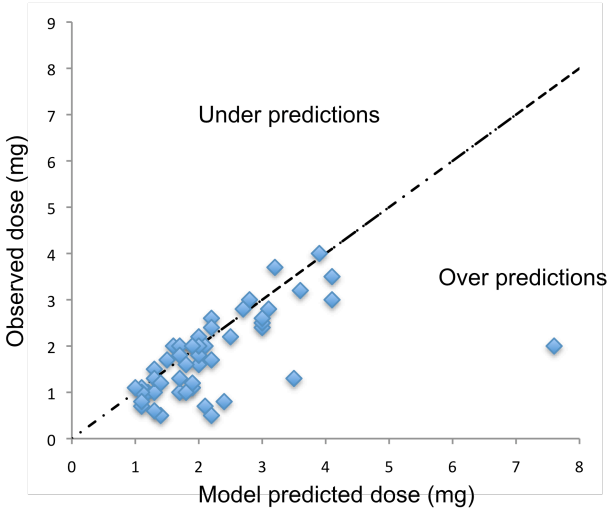

Figure 5. Observed vs. model predicted daily warfarin dose for the Japanese paediatric study population using the model predicted VKORC1 genotypes.

Conclusion

Simulations from the allometricly scaled KPD model gave results that were scientifically plausible, giving further support to use the model on paediatric data. Model predicted doses using the assigned VKORC1 genotypes agreed well with observed doses, with no evidence of model misspecification.

Acknowledgement

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