

Leveraging Prior Quantitative Knowledge Demonstrates the Importance of Genotype-based Dosing of Warfarin

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Introduction

Warfarin is the oral anticoagulant most frequently used for long-term prevention of thromboembolic events. The drug has a narrow therapeutic index and its optimal anticoagulation therapy requires achieving and maintaining a target International Normalized Ratio (INR). A significant number of factors play a role in achieving and maintaining the INR within its target range and a high between patient variability in therapeutic dose requirement has been observed.

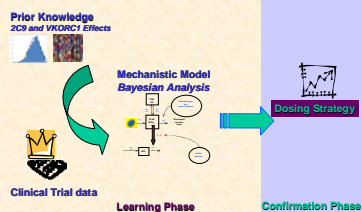
Objective

To leverage prior information on PK, PD and genetic variation, thereby optimizing warfarin dosing algorithm to be studied in future trials.

Methods

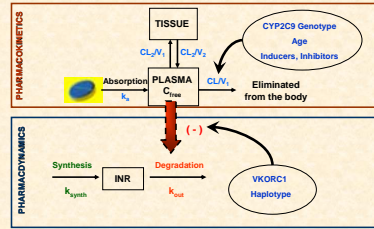
We performed a thorough literature search on information about warfarin therapy pertaining to metabolic variation due to factors such as weight, age and CYP2C9 genotype status; relationship between concentration-INR; and influence of VKORC1 genotype status on the IC50. The mechanistic concentration-INR relationship reported in the literature, together with the effects of known prognostic factors was employed to analyze data from a new study of 71 patients treated with warfarin up to 90 days. The model and the parameter estimates were utilized to explore competing dosing regimens. These regimens were compared using the proportion of patients below, within and above a target INR of 2-3.

Analysis strategy :



Analysis strategy for optimizing warfarin nomogram : We adopted a Bayesian approach to find an optimal warfarin dosing nomogram, which can integrate prior knowledge on warfarin mechanism and update our dosing algorithm as new data accrue.

Warfarin mechanistic model



Simulation strategy

- Step 1 :** Narrow down the choices to conduct more rigorous simulations/analysis
- Step 2 :** Simulate time course of INR for different combination of starting dose and titration scheme and tune a dosing regimen
- Step 3 :** Derive clinically relevant endpoints from the simulated data
- Step 4 :** Go back to step 1 if necessary to explore more choices

Dosing regimen explored

Starting dose (mg)*

	A/A	G/A	G/G
*1*1	3	4	5
*1*2	3	4	5
*1*3	2.5	2.5	4
*2*2	2	2	2.5
*2*3	2	2	2.5
*3*3	0.5	1.0	1.0

*Dosing based on Robert S. Kidd, Arthur F. Harralson (Shenandoah University)

Titration schemes

CR : titration scheme being used in a current study

INR < 2	15% increase from previous dose
2 <= INR <= 3	No adjustment
3 < INR < 4	10% decrease from previous dose
4 <= INR < 5	15% decrease from previous dose
5 <= INR < 6	20% decrease from previous dose
INR >= 6	50% decrease from previous dose

MDL: alternative more aggressive scheme

INR < 2	20% increase from previous dose (10 % increase for CYP2C9*3*3)
2 <= INR <= 3	No adjustment
3 < INR < 4	20% decrease from previous dose
4 <= INR < 5	25% decrease from previous dose
5 <= INR < 6	30% decrease from previous dose
INR >= 6	50% decrease from previous dose

Simulation conditions:

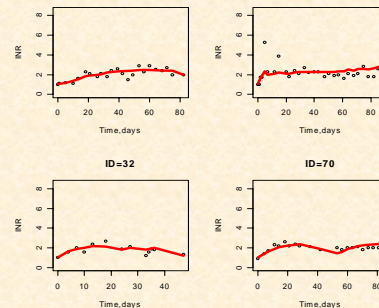
- 10,000 patients per arm
- Study period : 90 days
- Dose is given once / day and adjusted twice per week
- Starting dose (previous table) is given for the first 4 days
- From day 5, dose is adjusted based on the measured INR using a titration scheme

Results

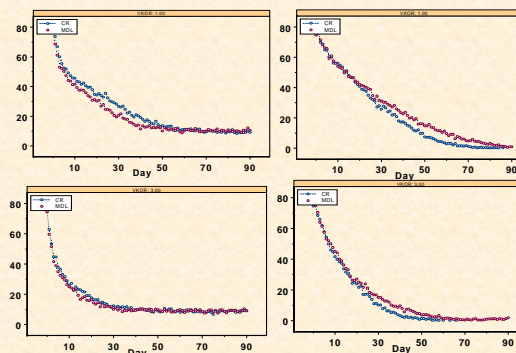
The mechanistic model described the time-course of INRs from the 71 patients well. We faced several challenges during this analysis, which ranged from conflicting literature reports, lack of PK data and variations on PK/PD model to wide disagreements on the IC50 estimates. The simulations suggest that CYP2C9 and VKORC1 genotype status play an important role in warfarin dosing. In addition, the choice of the warfarin titration strategy influences the time and the proportion of patients reaching and maintaining target INR.

Model fit

4 subjects were randomly chosen : dot: observed data, red line: model fit

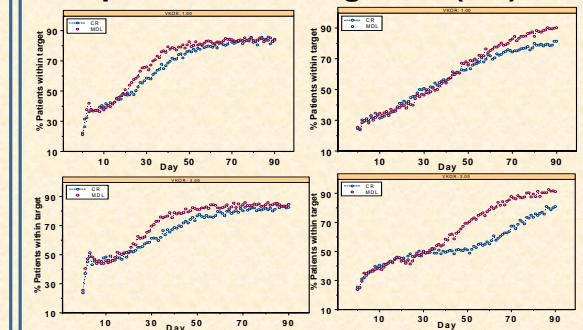


% of patients with INR < 2



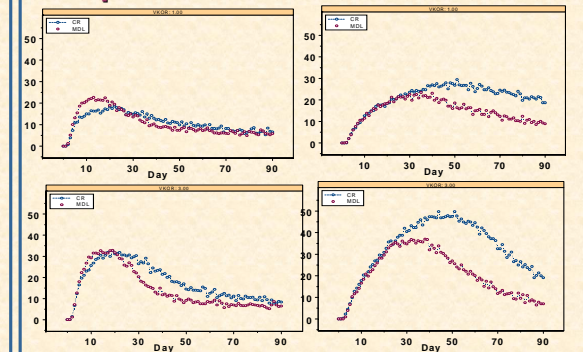
Above graphs show the percent of patients with INR < 2 at each time for the two different titration schemes with same starting dose. Top left : population with genotypes of VKORC1AA- CYP2C9*1*1, top right : VKORC1AA-CYP2C9*3*3, bottom left : VKORC1GG-CYP2C9*1*1, bottom right : VKORC1GG-CYP2C9*3*3

% of patients with target INR(2-3)



Above graphs show the percent of patients who reach target INR at each time for the two different titration schemes with same starting dose. Top left : population with genotypes of VKORC1AA- CYP2C9*1*1, top right : VKORC1AA-CYP2C9*3*3, bottom left : VKORC1GG-CYP2C9*1*1, bottom right : VKORC1GG-CYP2C9*3*3

% of patients with INR > 3



Above graphs show the percent of patients with INR > 3 at each time for the two different titration schemes with same starting dose. Top left : population with genotypes of VKORC1AA- CYP2C9*1*1, top right : VKORC1AA-CYP2C9*3*3, bottom left : VKORC1GG-CYP2C9*1*1, bottom right : VKORC1GG-CYP2C9*3*3

Conclusion

In silico modeling of prior quantitative information indicates that genotype based dosing and an optimized titration scheme play an important role in optimizing warfarin therapy.

References

- Hamberg et al ; CPT (2007)
- Chan et al ; CPT (1994)
- Robert S.Kidd and Arthur F.Harralson (Shenandoah University)