Clinical Application of a K-PD Warfarin Model for Bayesian Dose Individualisation in Primary Care

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Background

- Up to half of all patients that receive warfarin fail to reach and stay in their INR range[1].
- Adverse events associated with warfarin cost $984.9 million annually in Australia alone[2,3].
- Bayesian forecasting methods should increase the proportion of subjects in the therapeutic range.

Aim

To compare the probability of successful INR attainment using individualised warfarin dosing via Bayesian forecasting (DoseMe) and nomogram-based methods.

Methods

Dosing Methods

- A pre-existing K-PD model[4] was used to simulate a target INR of 1.8 - 3.2.
- Warfarin doses were adapted using DoseMe[5], a genotype-based nomogram and a non-genotype-based nomogram.
- The genotype-based nomogram adjusted initiation dose using genotype, with maintenance dose adjusted using genotype and INR response[6]. The non-genotype nomogram adjusted dose using INR response only[7,8].

The Adaptive Dosing Simulation Study

- 50 subjects were included in the simulation dataset, with simulated CYP2C9 and VKORC1 proportions representative of those previously observed[4]. The dataset was replicated 1000 times.
- The proportion of subjects with INRs in range was computed, with clinical trial results (CROWN study[6]) overlaid on the simulated results.

Results

Genotype Dosing Methods (Figure 1)

- At day 20 and 60, 42% [28 - 54%] and 76% [66 - 88%] (median, 95%CI) of subjects were expected to have an INR in range using the genotype nomogram-based dosing.
- At day 20 and 60, 56% [42 - 70%] and 74% [60 - 84%] of subjects were expected to have an INR in range using genotype Bayesian-based dosing.
- The observed clinical trial result for the genotype nomogram-based dosing was 66.7%[6], which was captured by the simulation model.

Non-Genotype Dosing Methods (Figure 2)

- At day 20 and 60, 38% [26 - 52%] and 40% [26 - 54%] of subjects were expected to have an INR in range using the non-genotype nomogram-based dosing.
- At day 20 and 60, 62% [46 - 76%] and 74% [62 - 86%] of subjects were expected to have an INR in range using non-genotype Bayesian-dosing.

Conclusions

- Non-genotype Bayesian dosing results in quicker and more accurate attainment of therapeutic INR when compared to non-genotype nomogram-based dosing.
- Genotype-based Bayesian dosing also resulted in quicker attainment of therapeutic INR compared to genotype nomogram-based dosing.
- Bayesian methods implemented in DoseMe provide an easy to use practical dosing solution that can negate the need for genotype testing.

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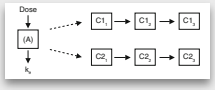
K-PD Model and Nomograms

K-PD Model[4]



$$\frac{dA}{dT} = -k_e \cdot A$$
$$\frac{dC1_1}{dT} = (1 - EFF) \cdot \frac{3}{MTT_{C1}} - C1_1 \cdot \frac{3}{MTT_{C1}}$$
$$\vdots$$
$$\frac{dC1_m}{dT} = C1_{m-1} \cdot \frac{3}{MTT_{C1}} - C1_m \cdot \frac{3}{MTT_{C1}}$$
$$\frac{dC2_1}{dT} = (1 - EFF) \cdot \frac{3}{MTT_{C2}} - C2_1 \cdot \frac{3}{MTT_{C2}}$$
$$\vdots$$
$$\frac{dC2_m}{dT} = C2_{m-1} \cdot \frac{3}{MTT_{C2}} - C2_m \cdot \frac{3}{MTT_{C2}}$$
$$k_e = \frac{CLs}{Vs}$$
$$DR = A \cdot k_e$$
$$EDK_{50} = CL \cdot EC_{50}$$
$$EFF = \frac{E_{max} \cdot DR^{\gamma}}{EDK_{50}^{\gamma} + DR^{\gamma}}$$

	Population Estimate	Between-subject Variability (%)
Kinetic Parameters		
CL (L/hr)	0.348	
Vc (L)	14.3	
KDE = CL/Vc (/hr)		58.9%
Pharmacodynamic Parameters		
Emax	1	
γ	1.15	
EC50 (mg/L)	4.10	34.0
MTT1 (hr)	28.6	
MTT2 (hr)	118.3	
Proportional residual error, σ (%)	20	

Genotype Nomogram[6]

Initiation Dosing

CYP2C9 Genotype \ VKORC1	A/A	A/B	B/B
*1*1	3.5	5	7
*1*2	3	4	4.5
*1*3	2.5	3	4
*2*2	1	1.5	2.5
*2*3	1	1.5	2.5
*3*3	1	1	1

Maintenance Dosing

INR	Dose adjustment relative to previous dose
INR < 1.8	20% increase (10% for CYP2C9 *3*3)
1.8 < INR < 3.2	No change
3.2 < INR < 4	20% decrease
4 < INR < 5	25% decrease
5 < INR < 6	30% decrease
INR > 6	50% decrease

Non-Genotype Nomogram[7,8]

Initiation Dosing

Day	INR	Dose
1	less than 1.4	5 mg
2	less than 1.8	5 mg
	1.8 - 2	4 mg
	greater than 2	Nil
3	less than 2	5 mg
	2 - 2.5	4 mg
	2.6 - 2.9	3 mg
	3 - 3.2	2 mg
	3.3 - 3.5	1 mg
	greater than 3.5	Nil
4	less than 1.4	10 mg
	1.4 - 1.5	7 mg
	1.6 - 1.7	6 mg
	1.8 - 1.9	5 mg
	2 - 2.3	4 mg
	2.4 - 3	3 mg
	3.1 - 3.2	2 mg
	3.3 - 3.5	1 mg
	greater than 3.5	Nil

After day 4, dosing is based on clinical judgement.

Maintenance Dosing

INR	Adjustment in total mg of warfarin per week
≤ 1.5	Increase 15% per week
1.51 - 1.99	Increase 10% per week
2 - 3	No change
3.01 - 4	Decrease 10% per week
4.01 - 4.99	Hold one dose; restart with dose decreased 10% per week
5 - 8.99	Hold until INR is 2 - 3; restart with dose decreased 15% per week

Results

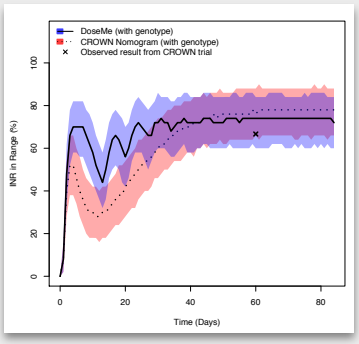


Figure 1: DoseMe (with genotype) vs Genotype Nomogram. Line shows the median percentage of patients in range, colour shows 95% CIs.

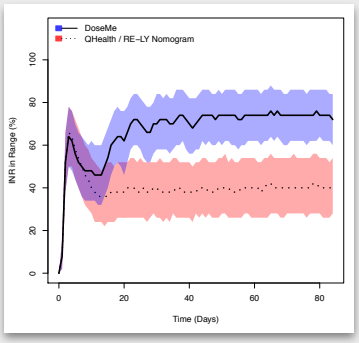


Figure 2: DoseMe vs Non-Genotype Nomogram. Line shows the median percentage of patients in range, colour shows 95% CIs.

References

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