

Predicting the Optimal Maintenance Dose of Warfarin Based on Multiple Influential Factors

¹Ahmed Elsafty, MD, SH(ASCPi); ²Maryana Gumenyak, MS, MLS; ²Elena Agranovsky, MD, PhD

¹SiParadigm Diagnostics Informatics, Pine Brook, NJ; ²Lenco Diagnostic Laboratories, Brooklyn, NY

Introduction

Warfarin is widely used for prophylaxis and treatment of different disease categories although there are new anticoagulant drugs.

The list of diseases includes:

- 1- Venous thrombosis,
- 2- Stroke and thromboembolism,
- 3- Genetic disorders as factor V Leiden thrombophilia,
- 4- Antiphospholipid antibody syndrome,
- 5- Cardiac valve replacement,
- 6- Post-myocardial infarction,
- 7- Rheumatic valve disease,
- 9- Cardioembolic stroke,
- 10- Systolic left ventricular dysfunction, and others.

The patients may also complain of systematic diseases on top; such as lupus thrombophilia, severe anemia, renal and hepatic diseases as well as drug interactions.

There are black box warnings from the FDA because the safety margin of Warfarin is narrow, requiring regular monitoring to avoid the unpredicted fatal bleeding and thrombophilia/embolisms.

The initial dose is adjusted depending on the Prothrombin Time - International Normalized Ratio (PT-INR) level to establish the maintenance dose.

The monitored adjustment may take several days with risk of unpredicted adverse effects.

Objective

To formulate a valid and reliable equation that indicates the daily maintenance dose of Warfarin "Marevan" which achieves closest PT-INR levels to the targets (INR 2.0-3.0)

Methodology

Studies were conducted on 150 adult patients (75 males and 75 females) treated with daily doses of Warfarin "Marevan" for different therapeutic/prophylactic indications with variable PT-INR results (1.15 - 12.7)

The samples were drawn at least two days after the drug initial administration. Laboratory tests were analyzed using fully-automated machines with reviewed quality control and preanalytical precautions.

	Marivan ml/day	INR	Alb. g/dL	Age Yrs	PCV %	Height cm	weight Kg	Total Alb. g/plasma vol.
Min.	1.0	1.15	2.9	30	30.1	150.0	60	77.3
Mean	4.3	2.8	3.8	63	37.6	165.5	85.3	112.0
Max.	15.0	12.7	4.8	91	46.2	187.0	130	170.9

A continuous multiple regression analysis was undertaken. The dependent variable was the daily Warfarin "Marevan" dose in milligrams.

Results

Multiple R	0.8155
R-squared	0.665
Adjusted R-squared	0.6421
p-value	3.892E-06

	Without Age	Without Total Alb	Without INR	Without cm	Without PCV	Without Kg	Without Alb
R	0.733	0.7418	0.7496	0.7514	0.753	0.7642	0.7869
p-value	0.00015	0.0001	6.8E-05	6.2E-05	5.7E-05	3.1E-05	8.0E-06

Correlation With Marevan	INR	Alb	Age	PCV	Kg	cm	Total Alb
	0.070	0.532	-0.480	0.361	0.126	0.060	0.418

Correlation With INR	Marivan	Alb	Age	PCV	Kg	cm	Total Alb
	0.070	-0.297	0.388	-0.258	0.084	-0.249	-0.164

Correlation with INR	Alb	Age	PCV	cm	Kg	Total Alb	Cases
CTRL: Normal Alb & INR	-0.069	0.014	-0.158	-0.101	-0.175	-0.222	28
CTRL: Low Alb & normal INR	-0.257	0.343	0.093	-0.131	0.224	-0.206	13
CTRL: Low Alb & high INR	-0.164	-0.228	-0.210	-0.155	0.166	-0.085	23

INR	Cases
1.15 – 1.5	21
1.51 – 2.0	19
2.01 – 3.0	51
3.01 – 5.0	27
5.01 – 10.0	24
> 10.0	8

Interpretations and Conclusion

Multiple regression analysis revealed significant results (multiple adjusted R-squared 0.6421 with minimal two sided p-values).

Conducting the multiple regression analysis with excluding one influential factor each time revealed that age, total plasma albumin then INR have highest significant influence on predicting the Warfarin "Marevan" maintenance dose.

Pearson correlation study revealed that Warfarin "Marevan" maintenance doses are proportional with total plasma albumin but inversely proportional with the age.

Thus, lower doses are effective in case of increased patient age or low albumin production. While in isolated anemia without albumin loss or low albumin production, higher doses are required.

A reliable equation was developed to predict the Warfarin "Marevan" dose which mostly achieves a PT-INR level of **3.0** or any targeted level:

$$\text{Predicted Warfarin "Marevan" dose} = + 50.925 + 0.761809 \times \text{PT-INR} [+ 0.761809 \times 3.0] - 6.5529 \times \text{Serum Albumin Concentration (g/dL)} - 0.090621 \times \text{Patient Age (Years)} + 0.533689 \times \text{Packed Cell Volume (Hematocrit)} - 0.322639 \times \text{Height (Centimeters)} - 0.241959 \times \text{Weight (Kilograms)} + 0.322824 \times \text{Estimated Total Plasma Albumin}$$

The equation encompassed almost two thirds of all potential variables, including the effect of other drugs interaction.

Clinical history and disease review revealed that the equation was applicable to cases with coexisting lupus thrombophilia, severe anemia, renal or liver diseases.

Limitations: in presence of moderate or severe cold agglutinins, the equation predicted underestimated doses.