Original Article
Yonsei Med J 2016 May;57(3):635-640
http://dx.doi.org/10.3349/ymj.2016.57.3.635
Yonsei Medical Journal
YMJ
pISSN: 0513-5796 · eISSN: 1976-2437

Development and Comparison of Warfarin Dosing Algorithms in Stroke Patients

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Purpose: The genes for cytochrome P450 2C9 (*CYP2C9*) and vitamin K epoxide reductase complex subunit 1 (*VKORC1*) have been identified as important genetic determinants of warfarin dosing and have been studied. We developed warfarin algorithm for Korean patients with stroke and compared the accuracy of warfarin dose prediction algorithms based on the pharmacogenetics.

Materials and Methods: A total of 101 patients on stable maintenance dose of warfarin were enrolled. Warfarin dosing algorithm was developed using multiple linear regression analysis. The performance of all the algorithms was characterized with coefficient of determination, determined by linear regression, and the mean of percent deviation was used to predict doses from the actual dose. In addition, we compared the performance of the algorithms using percentage of predicted dose falling within ±20% of clinically observed doses and dividing the patients into a low-dose group (≤3 mg/day), an intermediate-dose group (3–7 mg/day), and high-dose group (≥7 mg/day).

Results: A new developed algorithms including the variables of age, body weight, and *CYP2C9* and *VKORC1* genotype. Our algorithm accounted for 51% of variation in the warfarin stable dose, and performed best in predicting dose within 20% of actual dose and intermediate-dose group.

Conclusion: Our warfarin dosing algorithm may be useful for Korean patients with stroke. Further studies to elucidate clinical utility of genotype-guided dosing and find the additional genetic association are necessary.

Key Words: *CYP2C9*, Korean, stroke, *VKOC1*, warfarin

INTRODUCTION

Warfarin, the most commonly used oral anticoagulant in the world, is indicated for the prevention and treatment of thromboembolic events in patients with deep vein thrombosis, pulmonary embolism, atrial fibrillation and prosthetic heart valves. It is administered as a racemic mixture of S-warfarin and R-warfarin. S-warfarin is the more active isomer and has a greater therapeutic effect. These enantiomers are extensively metabolized by various cytochrome P450 enzymes. R-warfarin is mainly metabolized by cytochrome P450 1A2 (CYP1A2), CYP2C19, and CYP3A4, while S-warfarin is predominantly metabolized by CYP2C9.[1] Both enantiomers affect the coagulation cascade by inhibiting the activity of vitamin K epoxide reductase complex 1 (VKORC1), thus interfering with the activation of clotting factors II, VII, IX, and X.[2] However, despite its considerable benefit, warfarin is less frequently prescribed than it should be,[3] because of it's relatively high adverse event rate and the difficulty in managing the therapy.[4] Common adverse drug events (ADEs) arising from warfarin treatment include major and minor bleeding and hemorrhagic stroke.[5] ADEs are also frequently due to insufficient therapy: ischemic stroke and venous thromboembolism.[6] Warfarin, which has narrow therapeutic index, shows not only large inter-individual variations in dose response but also intra-individual variation. Because patients' clinical characteristics such as age, gender, body weight, concurrent medications, diet, co-morbidities

Received: April 14, 2015 **Revised:** August 4, 2015
Accepted: September 25, 2015
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•The authors have no financial conflicts of interest.

and patient compliance level have shown to have large influence on warfarin dosing,[7] frequent monitoring of its effect, as measured by the international normalized ratio (INR), is warranted.

CYP2C9 and *VKORC1* have been identified as important genetic determinants of warfarin dosing. The most common *CYP2C9* genotype among all ethnic is *CYP2C9*1* and found in about 80% of Caucasians[8] and 93% of Korean.[9] Lindh, et al.[10] demonstrated that carriers of *CYP2C9*2* and *CYP2C9*3* alleles require less warfarin dose than carriers of wild type *CYP2C9*1* genotype. Difference in allelic frequencies are also observed with the most common single nucleotide polymorphisms (SNPs) in the *VKORC1* gene, 1173C>T (rs9934438). Approximately, 35% of caucasians carry CC genotype, while only about 15% carry the TT genotype. However, most of the Korean showed TT genotype, but less than 1% carry CC genotype.[11] Carriers of 1173CC and 1173CT genotype need 44% and 97%, respectively, more warfarin dose than carriers of 1173TT genotype.[12] The clinical algorithms for determining warfarin dose containing clinical characteristics and pharmacogenetics information of the patients have been developed for more proper warfarin dose prediction. These algorithms are not intended to replace INR monitoring, but to increase the accuracy and reduce trial and error approach in warfarin dosing. According to International Warfarin Pharmacogenetics Consortium (IWPC) study,[13] the algorithms using clinical and genetic information increase the accuracy in dose prediction than a fixed-dose approach or algorithms derived from clinical information. In addition, they are useful, especially in the patients who may be administered more or less than appropriate dose.[13]

Personalized dosing and INR monitoring are required, because response to warfarin is different depending on the indication and the state of the disease. The studies on warfarin dose assessment so far was mainly targeted at valvular heart disease, deep vein thrombosis and atrial fibrillation.[13-21] On the other hand, warfarin is widely used to prevent the recurrence of stroke, which occupied the second place in the current causes of death in Korea, nevertheless, there are only a few studies to compare the predictive power of the dosing control based on a pharmacogenetics. This study reviewed prescribed dose and actual INR response in patients with stroke and compared the accuracy of 10 warfarin dose prediction algorithms based on the pharmacogenetics. In addition, warfarin dosing algorithm for Korean patients with stroke was developed to increase the quality of care for stroke patients.

MATERIALS AND METHODS

Study subjects

A total of 129 patients undergoing warfarin treatment for prevention and treatment of stroke and requesting genotyping of *CYP2C9* and *VKORC1* were recruited retrospectively at the neurology clinic at the Severance Hospital, Seoul, Korea. All study participants were enrolled between January 2009 and December 2014. Patients included were adults, whose warfarin dose requirement had remained constant for at least 3 previous clinic visits over a minimum period of 3 months, and with an INR of the prothrombin time within the range of 1.5 to 3.0.[22] Twenty-eight patients were excluded from the study according to enrolment criteria. This study was approved by the Institutional Review Board of the Yonsei University Severance Hospital, Seoul, Korea. Written informed consent was obtained from the patients.

Demographic and clinical data collection

Data were collected from patients' medical records. These data included demographic characteristics, comorbidities, the stable therapeutic dose of warfarin, the INR achieved with a stable warfarin dose, the use of concomitant medications, and the genotype of *CYP2C9* and *VKORC1*. The interacting drugs, which is defined based on previously published literature, were also reviewed.[23,24]

Genotyping

Genomic DNA was extracted from EDTA whole blood samples with QIAamp DNA Extraction Kit (Qiagen, Hilden, Germany). For determination of the *CYP2C9* genotype, the *CYP2C9*3* (1075A>C; rs1057910) SNP is selected. For *VKORC1* genotypes, the *VKORC1* 1173C>T (rs 9934438) SNP is determined. PCR and direct sequencing were performed using primers designed in Primer3 software (http://bioinfo.ut.ee/primer3-0.4.0/). Purified PCR products were obtained using a QIAquick Gel Extraction Kit (Qiagen, Düsseldorf, Germany) and were sequenced using a Big Dye Terminator Cycle Sequencing Ready Reaction Kit (Applied Biosystems, Foster City, CA, USA). Sequences were analyzed using an ABI 3500dx system (Applied Biosystems). To detect any sequence variation, the sequences were compared to the reference sequences using Sequencher software (Gene Codes, Ann Arbor, MI, USA).

Dosing algorithms

A literature search from Pubmed database was performed, with the search terms warfarin, algorithm, polymorphism, *CYP2C9* and *VKORC1*, to select warfarin dosing algorithms. Algorithms were included based on the following criteria; 1) equations to predict maintenance warfarin dose, 2) only two SNPs consisting of *VKORC1* 1173G>T (or *VKORC1* -1639G>A and 2255C>T) and *CYP2C9*2* and/or **3*, 3) published in English, 4) equations containing available clinical parameters, 5) algorithms were selected, depending on a historical aspect (e.g., the first warfarin dosing model), the size or ethnicity of the study population. Studies that enrolled adult patients with atrial fibrillation, venous thromboembolic diseases, recent orthopedic surgery, valvular disease, and stroke were also included. Wherever genotype is missing, we imputed its value based on other *VKORC1*

http://dx.doi.org/10.3349/ymj.2016.57.3.635

SNPs, because *VKORC1* 1173 genotype is suggested to be in complete linkage disequilibrium with *VKORC1* -1639 and 2255.[13,25]

Nine algorithms were selected from the literature that met our inclusion criteria. These are referred to as Sconce, et al.,[15] Anderson, et al.,[20] Gage, et al.,[14] Wu, et al.,[21] IWPC,[13] Wadelius, et al.,[17] Huang, et al.,[19] Ohno, et al.,[16] and Cho, et al.[18] throughout this manuscript.

Data analysis

Warfarin doses between the different genotypes were compared using the Mann Whitney U-test. Predictive accuracy was assessed by comparing the dose predicted by the nine algorithms to actual dose which the patient was taking. Predicted dose was calculated using published equations, except Gage's calculated by input on the website http://www.warfarindosing.org. A best fit trendline and correlation coefficient were determined by linear regression. In addition, the mean of percent deviation of predicted doses from the actual dose was used to evaluate the predictive accuracy of each algorithms. In addition, we compared the performance of the algorithms using percentage of predicted dose falling within ±20% of clinically observed doses[26] and dividing the patients into low-dose group (≤3 mg/day), intermediate-dose group (3–7 mg/day), and high-dose group (≥7 mg/day).[13] Stepwise multiple regression analysis was performed to develop new warfarin dosing algorithm, and the results of univariate analysis were used to choose predictors for multivariate analysis. All statistical tests were performed with a p value<0.05 significance. All analyses were performed using the Statistical Package for Social Science (SPSS 18.0; SPSS Inc., Chicago, IL, USA).

RESULTS

Characteristics of the study groups

The characteristics of all 101 patients are listed in Table 1. A total of 101 patients with a mean age 64 years (SD, ±13.4) ranging from 27 to 88 years, included 64 males (63%). The mean body weight was 64.6 kg (SD, ±10.5), and the mean body surface area was 1.7 (SD, ±0.2). The mean stable warfarin dose was 3.74 mg/day (SD, ±1.43). Concurrent diseases associated with these patients included atrial fibrillation (63 patients, 62%), hypertension (52 patients, 52%), diabetes mellitus (27 patients, 27%), heart disease including coronary arterial occlusive disease (14 patients, 14%), heart failure (7 patients, 7%), and cardiac valvular disease (9 patients, 9%). Other sources of cardioemboilism including patent foramen ovale and left atrial thrombus were identified, in addition to heart problem that is shown in the Table 1. A total of 44 (44%) patients were receiving comedication that could affect the anticoagulation effect of warfarin, including amiodarone, aspirin, antiplatelet drugs, statins, thyroid hormone, and verapamil.

Effects of genotype on stable dose of warfarin

Table 2 shows daily warfarin dose of different genotypes. For *CYP2C9*, 97 patients (96%) were identified to be homozygous for *CYP2C9*1*, and 4 patients (4%) were heterozygous for *CYP2C9*3*. No patients with *CYP2C9*2* allele were identified. The frequency of the *VKORC1* 1173TT genotype was 82% and that of 1173CT genotype was 17%, and only 1 patient was homozygous for the variant C allele. In our study, no patients with homozygous *CYP2C9*3/*3* were identified, and the *CYP2C9* and *VKORC* SNPs for Korean were in Hardy-Weinberg equilibrium. The stable warfarin doses for patients with *VKORC1* TT type (3.6±1.2 mg/day) were significantly lower than those for patients with any other *VKORC1* genotype (p<0.05). However,

Table 1. Characteristics of the Study Population

Variables	n=101
Men (%)	64/37 (63/37)
Mean age (SD) (range), yr	63.6 (13.4) (27–88)
Body weight (SD) (range), kg	64.6 (10.5) (44–90)
Mean BSA (SD) (range), m^2	1.7 (0.2) (1.3–2.1)
Smoking patients (%)	31/101 (31)
Concurrent disease (%)	
Atrial fibrillation	63/101 (62)
Cancer	1/101 (1)
Cardiac valvular disease	9/101 (9)
Cervicocephalic artery dissection	5/101 (5)
CHF/cardiomyopathy	7/101 (7)
CAOD	14/101 (14)
Diabetes mellitus	27/101 (27)
Hypertension	52/101 (52)
Hyperthyroidism	2/101 (2)
Hypothyroidism	1/101 (1)
Comedication	
Amiodarone	4/101 (4)
Aspirin	36/101 (36)
Antiplatelet drug	14/101 (14)
Statins	70/101 (69)
Thyroid hormone	1/101 (1)
Verapamil	24/101 (24)

BSA, body surface area; CHF, congestive heart failure; CAOD, coronary arterial occlusive disease.

Table 2. Effects of *VKORC1* 1173C>T and *CYP2C9* Genotypes on Warfarin Stable Dose

Genotype	n	Warfarin dose (mg/day)	p value
VKORC1 1173			<0.05
CC	1	6.0	
CT	17	4.6±1.9	
TT	83	3.6±1.2	
*CYP2C9*3*			0.080
**1/*1*	97	3.8±1.4	
**1/*3*	4	2.6±0.5	
**3/*3*	0		

the difference in the stable warfarin dose between patients with homozygous for *CYP2C9*1* (3.8±1.4 mg/day) and heterozygous for *CYP2C9*3* (2.6±0.5 mg/day) was not significant.

Establishing of dosing algorithm

For multiple linear regression analysis, 4 variables, including age, bodyweight, *CYP2C9*3* and *VKORC1* 1173 genotypes, were selected (R^2=0.51) (Table 3). We established the warfarin dosing formula with following equation: maintenance dose=exp [1.756-0.015 (age)+0.006 (body weight)-0.284 (*CYP2C9* genotype)+0.407 (*VKORC1* genotype)]. It was coded as 1 in the case of the presence of the *CYP2C9* variant, or the presence of the *VKORC1* 1173C allele.

Dosing algorithm comparison

A comparison of the ten algorithms for determining warfarin doses is shown in Table 4. Most algorithms that evaluated, including the dosing algorithm derived from this study, had a good correlation. However, the algorithms by Gage, et al.,[14] Wu, et al.,[21] and Huang, et al.[19] showed poor correlation. Among these 7 algorithms, algorithms from this study, Sconce, et al.,[15] Anderson, et al.,[20] and Ohno, et al.[16] produce similar accuracy with mean deviation ranging from -10.0 to 4.3. These algorithms were selected based on their correlation coefficient (r> 0.6) and the mean deviation from the actual dose (mean deviation about 10%) for further analysis. The algorithm from this study provided significantly better prediction fell within 20% of the actual dose (Table 5). Others performed similarly to predict ideal dose. Algorithms by Sconce, et al.[15] and Ohno, et al.[16] tend to underestimate in about 40% of cases. In addition, the accuracy of this study and Anderson, et al.[20] was better than others for patients who need intermediate-dose group (Table 6). For patients who need less than 3 mg/day, algorithm by Ohno performed well. However, for patients who required more than 7 mg/day, all algorithms performed poorly, with underestimation for all patients.

Table 3. Contribution of Individual Variables to the Algorithm

Variables	R (R^2_{adj})	Slope (beta)	Standard error	*p* value
All	0.73 (0.51)			
Age	0.58 (0.33)	-0.15	0.002	<0.001
Body weight	0.01 (0)	0.006	0.003	0.017
CYP2C9	0.02 (0.01)	-0.284	0.134	0.037
VKORC1	0.13 (0.17)	0.407	0.069	<0.001

R^2_{adj}, R^2 adjusted.

DISCUSSION

Warfarin, the first human anticoagulant, remains the most commonly prescribed oral anticoagulant in the world. Warfarin exerts its effect by inhibiting the activity of *VKORC1*, thus interfering with the activation of vitamin K-dependent clotting factors II, VII, IX, and X.[2] Warfarin is underutilized for stroke prevention. The Agency for Healthcare Policy and Research noted that physicians avoid to prescribe warfarin, because they are not familiar with techniques for administrating the drug safely and fear bleeding complication.[3,4] Warfarin therapy is

Table 5. Percentage of Patients with an Ideal, Underestimated, or Overestimated Dose of Warfarin as Estimated by Each Algorithm

Algorithm	Ideal dose* (%)	Underestimation (%)	Overestimation (%)
This study	53	22	26
Anderson, et al.[20]	50	20	31
Sconce, et al.[15]	46	40	15
Ohno, et al.[16]	46	42	13

*Predicted doses falling within ±20% of clinically observed doses.

Table 6. Sensitivity Analysis with Low-, Intermediate-, and High-Dose Patient Groups

Algorithm	Subgroups based on the warfarin dose		
	≤3 mg/d (n=50)	>3, <7 mg/d (n=48)	≥7 mg/d (n=3)
This study	48	63	0
Anderson, et al.[20]	40	63	0
Sconce, et al.[15]	52	42	0
Ohno, et al.[16]	62	31	0

Table 4. Comparison of the Warfarin Dosing Algorithms

Algorithm	Derivation sample (n)	R	R^2 (R^2_{adj})	Mean deviation (%)	Regression equation
This study	101	0.73	0.53 (0.51)	3.3	y=0.406x+1.886
Gage, et al.[14]	1015	0.57	0.33 (0.32)	-7.1	y=0.453x+1.546
Sconce, et al.[15]	297	0.62	0.38 (0.38)	-9.9	y=0.394x+1.676
Wu, et al.[21]	92	0.36	0.13 (0.12)	46.4	y=0.208x+4.105
Anderson, et al.[20]	213	0.69	0.48 (0.47)	4.3	y=0.301x+2.427
Ohno, et al.[16]	125	0.65	0.42 (0.41)	-10.0	y=0.316x+1.913
Huang, et al.[19]	266	0.49	0.24 (0.23)	-16.9	y=0.237x+1.940
Wadelius, et al.[17]	1496	0.63	0.40 (0.39)	50.8	y=0.360x+3.748
IWPC[13]	4043	0.61	0.37 (0.37)	-17.9	y=0.324x+1.634
Cho, et al.[18]	130	0.64	0.41 (0.41)	-49.7	y=0.094x+1.336

R^2_{adj}, R^2 adjusted.

http://dx.doi.org/10.3349/ymj.2016.57.3.635

challenging, because warfarin has narrow therapeutic index. In addition, it shows not only large inter-individual variations in dose response but also intra-individual variation. Because patients' clinical characteristics such as age, gender, body weight, concurrent medications, diet, co-morbidities and patient compliance level largely influence warfarin dosing,[7] frequent monitoring of its effect, as measured by the INR, is warranted.

CYP2C9 and *VKORC1* have been identified as important genetic determinants of warfarin dosing. Two prospective studies[20,27] on genotype-guided warfarin dosing predicted more accurately, resulting in reduction of dosing changes, minor bleeding complication, and time to reach therapeutic range. Although numerous warfarin dosing algorithms have been developed, their indications for warfarin usage were heterogeneous. Until now, there has been no consensus pharmacogenetic-guided algorithm.

In the present study, we developed an algorithm to provide a practical warfarin dosing for Korean patients with stroke. The warfarin dosing algorithm was developed on a homogeneous population and single disease indication for stroke, since warfarin have been underused for prevention of stroke and there are few studies on warfarin dosing algorithm focused on stroke patients. Because the distribution of warfarin dose is skewed, we created dosing algorithm for log transformation of doses, as evidenced by a mean percent deviation that was lower than that for both the raw doses square root of doses. Other variables including age and body weight showed normal distribution. We analyzed whether ten selected dosing algorithms, including the algorithm derived in the present study, could accurately predict warfarin dose in the study population, and found that the present algorithm demonstrated good correlation with actual dose, with coefficient of determination (R^2) of 0.51. Algorithm in this study is consisted of five factors; age, body weight, and genotypes of *CYP2C9* and *VKORC1*. While reduced incorporated factors are convenient for physicians to use, this algorithm performed better than Gage, et al.,[14] Wu, et al.,[21] and Huang, et al.[19] The *VKORC1* and *CYP2C9* genotypes accounted for about 14% of the inter-individual variation of the maintenance daily warfarin dose. Because allele frequencies of *VKORC1* and *CYP2C9* are different depending on race, the R^2 values of these genes differ among studies.

Anderson, et al.,[20] Ohno, et al.,[16] and Sconce, et al.[15] also showed good linear relationship with actual dose and predicted dose. However, the R^2 indicated the linearity of the association only, and the mean deviation from actual dose is a better measure of the algorithms' performance. Although the above three algorithms showed a good correlation with the actual dose in our study population, a better prediction of dosage was achieved by our model.

The algorithm devised by Cho, et al.[18] was the latest warfarin dosing algorithm for Korean patients with atrial fibrillation and the best model for prediction of daily maintenance dose. This algorithm showed a good relationship between the actual dose and the predicted warfarin dose in our study population as reported previously. However, this algorithm was the worst performing algorithm by means of the mean deviation. The mean age, the strongest predictor of warfarin dose, was slightly older in cohort of Cho, et al., although its significance is unclear. Because these two algorithms developed for two different single disease indication; atrial fibrillation and stroke, these patients may be differently influenced by environmental factors such as coadministered drugs and comorbidities. Atrial fibrillation was indeed the most common indication of warfarin usage in this study. Likewise western countries,[28] cervicocephalic artery dissections were common causes of stroke in young patients under 45. Cho, et al.[18] reported that statin influences the daily dose of warfarin. Simvastatin, fluvastatin, and lovastatin potentiate warfarin's effect.[24,29] In our study, most patients were taking statin such as atorvastatin, pitavastatin, and rosuvastatin which do not affect the warfarin's effect. There is no correlation between daily dose of warfarin and statin status regardless of types of statin.

The algorithm derived in the present this study was less predictable among patients who required high doses of warfarin (≥7 mg/day). As this study was a small retrospective analysis with only a few patients requiring high doses, the results might have been skewed because of the individual patients variations. About 3% of the patients could have complication due to underdose. Of the three outliers, two patients were *VKORC1* CT genotype. The other was TT type and he was taking antituberculosis drug. Rimfampin decreases INR increase via induction of hepatic metabolism of warfarin.[24] Removal of these three data points did not improve the correlation coefficient for our algorithm (R^2=0.51). However, the sample size was too small to make a conclusion on the efficacy of the dosing algorithms in this population.

In this study, we found 0 and 4% prevalence of *CYP2C9*2* and *CYP2C9*3*, respectively, which is consistent with the report of Cho, et al. who also found no *CYP2C9*2* and a 8.5% prevalence of **3*. For *VKORC1*, we found 82%, 17%, and 1% prevalence of *VKORC1* TT, CT, CC genotype, respectively, which compares with the report of Cho, et al. who found 75.4%, 23.1%, and 1.5%, respectively.

Our study has several limitations. First, we did not have sufficient data to include potentially important factors such as vitamin K intake or compliance of administration even if we educated the patients when starting warfarin. However, the percentage of variability in warfarin dosing in our study is similar to that in other compared models, therefore, the effect of these variables is probably small. Second, because we investigated only one *VKORC1* SNPs, requiring us to impute missing genotype for evaluating some models. Therefore, we substituted missing genotype based on linkage disequilibrium, which is generally reliable.[25] Nevertheless, it may cause error that would lead to decrease of the accuracy of our model. Third, only

4% of the study population was younger than 40 years of age; therefore, additional models for stroke patients with younger age are needed, as age is important factor of prediction.

In order to further improve dosing algorithms, additional study is necessary in efforts to find new genes and SNPs contained with these genes that influence warfarin pharmacokinetics and pharmacodynamics. Although the incorporation of additional variables could improve predictive algorithm, the gains may be modest and probably do not justify the cost effectiveness and improvement of clinical outcome. In addition, studies on clinical utility of these pharmacogenetic-guided algorithms should be performed.

In conclusion, we developed warfarin dose prediction algorithm for patients with stroke, and it explained 51% of the variation in the daily maintenance warfarin dose. Further studies to elucidate clinical utility of genotype-guided dosing and find additional genetic association are necessary.

ACKNOWLEDGEMENTS

This study was supported by a grant of the Korean Health Technology R&D Project, Ministry of Health & Welfare, Republic of Korea (A120030).

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http://dx.doi.org/10.3349/ymj.2016.57.3.635