Comparison of Temporary Interruption of Warfarin Therapy for 3 and 5 days before Surgery in Thailand: A Randomized Controlled Trial

Angsu Chartrungsan, M.D.*, Pansak Laksanabunsong, M.D.*, Akarin Nimmannit, M.D., Bundarika Suwanawiboon, M.D.***, Naravat Poungvarin, M.D.****, Wanchai Wongkornrat, M.D.*, Kriangkrai Tantiwongkosri, M.D.*, Worawong Slisatkorn, M.D.*, Pranya Sakiyalak, M.D.*, Punnarerk Thongcharoen, M.D.*, Thaworn Subtaweesin, M.D.*, Somchai Sriyoschati, M.D.*, Teeravit Phanchaipetch, M.D.***

**Department of Surgery, **Routine to Research Unit, ***Department of Internal Medicine, ****Department of Clinical Pathology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.*

ABSTRACT

Objective: The ACCP guideline 2008 recommended cessation of warfarin five days before surgery. However, based on the observation of the clinical practice at Siriraj Hospital, we suggested a shorter period of three days before surgery. Prior studies have shown multiple factors had effected warfarin dosage, but few studies have shown factors that influenced normalization of prothrombin time after discontinuation of warfarin. Previous studies have shown the genetics factors, vitamin K epoxide reductase (VKORC1) and cytochrome P450 2C9 (CYP2C9) enzyme conjointly determine the warfarin maintenance dose. We wanted to find out the proper timing of warfarin cessation before surgery and relationhip to genetic factors.

Methods: Sixty-eight patients on warfarin were randomized to stop warfarin for three or five days. Blood samples were acquired at three or five days after interruption of warfarin in each group and assayed for INR, VKORC1 and CYP2C9. We started bridging therapy when INR was less than 2.0 and accepted an INR value of 1.5 or less on the day of surgery.

Results: A total of 68 patients were enrolled in the study. Thirty-three patients (48.5%) were male. The mean age was 50.8 ± 6.6 years (range 16-88 years). The mean BMI was 22.5 ± 3.6 kg. All patients had mechanical heart valve replacement, and 22 (32.4%) patients had AF. The mean cumulative weekly dose of warfarin was 27 ± 11.3 mg and baseline INR was 2.4 ± 0.3. Thirty (88.2%) patients in the three days group had INR ≤ 1.5 and thirty-three (97.3%) patients in the five days group had INR ≤ 1.5. There was no significant difference between interruption of warfarin for three and five days (p =0.16). Female sex, BMI and weekly warfarin dosage were associated to the longer cessation of warfarin. Only weekly warfarin dosage was a significant factor after multivariate analysis. From 68 patients, CYP2C9 *1/*1 was found in 93% and CYP2C9 *1/*3 was found in 7%. Neither mutant CYP2C9*2 allele nor individuals homozygous for CYP2C9*3 were observed. Regarding VKORC1, haplotype AB was found in 32% and haplotype AA was found in 63%. Haplotype BB (wild type) was found in 4%. Five patients who had INR > 1.5 after interruption of warfarin had VKORC1 haplotype AA, four patients had CYP2C9*1/*1 and one patient had CYP2C9 *1/*3. Neither VKORC1 nor CYP2C9 was related to normalization of INR (p=0.10, p=0.17).

Conclusion: Temporary interruption of the warfarin therapy between three days and five days with bridging therapy before surgery is not significantly different in the Thai population. This study recommends discontinuing warfarin three days before surgery. The proper timing of interruption for warfarin does not only depend on the half-life of warfarin but also depends on age, co morbidity, sex, BMI, lower maintenance warfarin dose, and concomitant drugs. If patients have cardiac or liver disease, they may spend longer time to discontinue warfarin before surgery.

Keywords: Warfarin, interruption, surgery, anticoagulant, cessation

Siriraj Med J 2013;65:69-72
E-journal: http://www.sirirajmedj.com

INTRODUCTION

Warfarin is the most widely prescribed oral anticoagulant. Approximately 2 million people in the U.S. start taking warfarin each year. It is used for the prevention and treatment of thrombosis and embolism. The perioperative management of patients taking vitamin K antagonists (VKAs) poses significant challenges for health care providers. It has been estimated this affects approximately 250,000 patients annually and the number of patients requiring chronic anticoagulation continues to increase.

Recent advances in understanding warfarin pharmacology have been made. Besides well-known demographic or environmental factors (advanced age, vitamin K intake,

Correspondence to: Pansak Laksanabunsong
E-mail: Lakkhana Naksawat
Received 15 November 2012
Revised 26 February 2013
Accepted 11 March 2013

concomitant drugs, co morbid conditions and acute illness) genetics single nucleotide polymorphisms (SNPs) have been identified as strongly affecting the maintenance dosage and its variability.

Polymorphisms in two genes, *CYP2C9* (cytochrome P_{450} 2C9) and *VKORC1* (vitamin K epoxide reductase complex, subunit 1) account for most of the genetic contribution to variability in warfarin response. *CYP2C9* variants affect warfarin pharmacokinetics. *VKORC1* variants affect warfarin pharmacodynamics.

Common variations in the *CYP2C9* gene, designated *CYP2C9*2* and **3*, encode an enzyme with decreased activity, and thus are associated with higher drug concentrations and reduced warfarin dose requirements. At least one variant allele of *CYP2C9*2* or *CYP2C9*3* is present in approximately 25% of European-Americans, but these variants are relatively uncommon in African-Americans and Asian populations. Heterozygosity for *CYP2C9*2* or **3* decreases the dose of warfarin required for anticoagulation by approximately 20-30% compared to "wild type" individuals (*CYP2C9 *1/*1*). Homozygosity for *CYP2C9*2* or **3* can decrease the warfarin dose requirement by approximately 50-70%. Generally the **3* allele has a greater effect than **2*.

VKORC1 recycles vitamin K epoxide to vitamin K hydroquinone, an essential factor for the formation of clotting factors II, VII, IX and X, and it is the target of Coumadin anticoagulants (such as warfarin). Several genetic variations in *VKORC1* are in strong linkage disequilibrium and have been designated haplotype A and B (or non-A). *VKORC1* variants are more prevalent than those of CYP2C9. The prevalence of *VKORC1* genetic variants is higher in Asians, followed by European-Americans and African-Americans. Polymorphisms in *VKORC1* may explain approximately 30% of the variability in warfarin dose requirements. Compared to *VKORC1* non-A/non-A homozygote, warfarin dose is decreased by approximately 25% in heterozygote and 50% in A/A homozygote.

Although previous studies have reported the genetic polymorphisms in CYP2C9 and VKORC1 to affect the dose requirement of warfarin, no study has shown influence for the clearance of it. The American College of Chest Physicians (ACCP) published the 8th edition of evidence-based guidelines for the perioperative management of antithrombotic therapy and they recommended stopping warfarin approximately five days before surgery with or without bridging therapy depending on risk of bleeding and thromboembolism.

Reference to many recent studies has shown the incidence of CYP2C9 *2 and *3 alleles are approximately 1% and 5-7% respectively in East Asians. The prevalence of VKORC1 non-A/non-A homozygote, heterozygote and A/A homozygote are approximately 7%, 30% and 63% respectively. The previous study from Chiangmai university showed the most frequently prevalent polymorphisms in northern Thai population are CYP2C9*1/*1 genotype (95%) and A/A haplotype (63.6%) which are classified in rapid metabolizer and low dose groups compared to Caucasians and African-Americans which have slightly less in CYP2C9*1/*1 genotype (70%, 90%) and lesser A/A haplotype (18%, 6%), which are classified in rapid metabolizer and high dose groups.

Due to less maintenance dose of warfarin required and lower average INR between Thai and Caucasian we hypothesized that there should be a shorter time to normalization of INR. In our experience at Siriraj hospital after discontinuing warfarin for approximately three days before surgery, most patients achieved normalization of prothrombin time (INR≤1.5). In this study we aimed to identify the effect after stopping warfarin for three days and five days in Thai patients who required surgery.

MATERIALS AND METHODS

Patients population

The study considered 68 Thai patients undergoing surgery with who had been on warfarin therapy with a goal of INR (2-3) for at least six months. The patients who had history of cirrhosis Child C, chronic kidney disease, heparin induced thrombocytopenia, INR < 2 or > 3.5 before interruption of warfarin, adjusted warfarin dose within 6 months, concomitant drugs Amiodarone, Diltiazem, Fenofibrate, Aspirin, Ciprofloxacin, Cotrimoxazole, Erythromycin, Fluconazole, Isoniazid, or Metronidazole were excluded from the study. All patients provided written informed consent after the study was approved by the Ethics Committee on Human Research, Faculty of Medicine Siriraj Hospital.

Study design

This was a randomized controlled-trial study. Sixty-eight participants were enrolled at a single center which was Siriraj Hospital. They were divided into two groups; the patients' warfarin had to be stopped three and five days before anticipated surgery in each group. Blood samples were drawn from all patients using a standard technique for routine preoperative lab which included coagulogram and another 5 ml were drawn for genetic analysis. The normalization of the prothrombin time, expressed as International Normalization Ratio (INR≤1.5) was used as an indicator of re-establishment of normal hemostasis. The aim of this study was to find out the proper timing of warfarin cessation before surgery and relationship to genetic factors.

Clinical Data

Baseline demographic data were collected about all patients as follows : patients characteristics – age, sex, body mass index (BMI) and information regarding liver disease based on previous diagnosis and/or concurrent laboratory results about serum levels of albumin, bilirubin and liver transminases together with warfarin related data – maintenance dose of warfarin (mean, mg/week) 6 months before surgery, baseline INR value, interval between the last dose of warfarin and time of blood drawing, preoperative INR plus concomitant medication in addition to readily available laboratory data on CBC, creatinine, LFT and coagulogram.

Statistical analysis

Subject characteristics were described using descriptive statistics, including means, standard deviation, median, minimum and maximum, frequencies and percentages. The normality of the distribution of the variables was examined with the Chi-square test. Logistic regression analysis was applied to explore factors associated with the normalization of INR. Variables, which were found to be significant in univariate analysis, were further entered into a multivariate model. For all tests performed, a two tailed p-value < 0.05 was considered as statistical significance. The statistical software SPSS, version 13.0 was used for all the analyses performed.

RESULTS

A total of 68 patients were included in the study. Thirty-three patients (48.5%) were male. The mean age was 50.8±6.6 years (range 16-88 years). The mean BMI was 22.5±3.6 kg/m^2. All patients had mechanical heart valve replacement, and 22 (32.4%) patients had AF (Table 1). The mean cumulative weekly dose of warfarin was 27±11.3 mg and baseline INR was 2.4±0.3. The mean cumulative weekly dose of warfarin was 26.8±11.0 mg in the three days group and 27.2±11.7 in the five days group. The baseline INR was 2.5±0.3 in the 3 days group and 2.4±0.3 in the 5 days group. The mean INR after interruption of warfarin for three days and five days were 1.4±0.2 and 1.3±0.1 respectively. Thirty (88.2%) patients in the three days group had INR ≤ 1.5 and thirty-three (97.3%) patients in the five days group had INR ≤ 1.5. There was no significant difference between interruption of warfarin at three and five days (p = 0.16) (Table 1). Four patients who had INR more than 1.5 after interruption of warfarin for 3 days were female, their mean age was 46.5±4.7 years old, mean BMI was 19.4±1.1 kg/m^2, mean weekly warfarin dose was 14.5±4.3 mg, mean baseline and interrupted INR was 2.4±0.3 and 1.8±0.3 respectively. One of them had cirrhosis child B and the other one had severe TR. Only one woman had INR more than 1.5 in the five days group, she was 50 years old with severe TR, BMI was 19.2 kg/m^2, weekly warfarin dose was 21 mg, baseline INR was 2.46 and after cessation for five days was her INR was 1.56. Female sex, BMI and weekly warfarin dose were associated with the longer cessation of warfarin (p=0.02, p=0.04, p=0.02). Only weekly warfarin dose was a significant factor after multivariate analysis (p=0.03) (Table 2).VKORC1 haplotype AA was found 63%, haplotype AB was found 32% and haplotype BB was found 4%. CYP2C9 *1/*1 was found 93% and *1/*3 was found 7%. Five cases that had INR > 1.5 after interruption of warfarin, were VKORC1 haplotype AA and four cases were CYP2C9*1/*1 and one case was CYP2C9 *1/*3. Neither VKORC1 nor CYP2C9 was related to normalization of INR (p=0.10, p=0.17) (Table 3). All patients underwent minor surgery (dental procedures and local excision) without hemorrhagic or thromboembolic complications.

DISCUSSION

In this study we have shown that 88% of the patients in this study had INR ≤ 1.5 after cessation of warfarin for three days and no significant difference from five days. Five patients who had INR more than 1.5 after interruption of warfarin therapy were postponed surgery until INR ≤ 1.5. The lower weekly warfarin dose was the only variable that was independently associated with a slow return to normal hemostasis. Age, sex, BMI, baseline INR and genetics could have been expected to influence the rate of normalization, but were not independent predictors.

Our results differ somewhat from those published by Hylek et al.[10] They found that in addition to lower maintenance dose of warfarin, also the baseline ("index") INR, age, decompensation for congestive heart failure and active cancer prolonged the normalization. Their population was, however, quite different, defined by excessive baseline INR of > 6.0 and not planned for surgery. MJ Kovacs et al., reported that 93% of two hundred and twenty two patients had INR ≤ 1.5 after cessation of warfarin for 5 days. They found that only baseline INR was an independent predictor of slow normalization of INR[5].

TABLE 1. Characteristics of patients enrolled in the study and patients who were assigned to interruption warfarin 3 and 5 days.

Characteristics	All	Group		p-value
		3 days	5 days	
N (%)	68 (100)	34 (50)	34 (50)	
Sex, males (%)	33 (48.5)	17 (50.0)	16 (47.1)	0.81
Age	50.8 ± 6.6	51.0 ± 6.4	50.65 ± 6.9	0.83
BMI	22.5 ± 3.6	22.7 ± 3.6	22.2 ± 3.5	0.54
Indication				
Mechanical valve (%)	68 (100)	34 (50)	34 (50)	
AF (%)	22 (32.4)	9 (13.2)	13 (19.1)	0.44
Weekly warfarin dose (mg)	27.0 ± 11.3	26.8 ± 11.0	27.2 ± 11.7	0.89
Baseline INR	2.4 ± 0.3	2.5±0.3	2.4±0.3	0.80
INR after stop warfarin	1.3 ± 0.2	1.4 ± 0.2	1.3 ± 0.1	<0.01
INR ≤ 1.5 (%)	63 (92.6)	30 (88.2)	33 (97.1)	0.16

TABLE 2. Characteristics of patients who achieved the target INR (≤1.5) after interruption of warfarin therapy.

Characteristics	INR ≤ 1.5	INR > 1.5	Univariate p-value	Multivariate p-value
N (%)	63 (92.6)	5 (7.4)	-	-
Sex, females (%)	30 (47.6)	5 (7.4)	0.02	-
Age	51.1 ± 6.7	47.2 ± 4.3	0.20	-
BMI	22.7 ± 3.6	19.4 ± 0.9	0.04	0.11
Indication (%)				
Mechanical valve	63 (92.6)	5 (7.4)	-	-
AF	20 (31.7)	2 (2.9)	0.20	-
Weekly warfarin dose	27.9 ± 11.2	15.8 ± 4.8	0.02	0.03
Baseline INR	2.4 ± 0.3	2.4 ± 0.2	0.69	-
INR after stop warfarin	1.3 ± 0.1	1.7 ± 0.2	0.00	-

TABLE 3. The allelic frequency distribution of variant CYP 2C9 and VKORC1 genotype.

Characteristic	All (%)	Group		Weekly warfarin dose (mg)	INR > 1.5 N=5 (%)	p-value
		3 days (%)	5 days (%)			
VKORC1						
AA	43 (63.2)	22 (32.4)	21 (30.9)	21.9 ± 8.8	5 (100)	0.10
AB	22 (32.4)	10 (14.7)	12 (17.7)	34.0 ± 4.3	-	
BB (wild)	3 (4.4)	2 (2.9)	1 (1.5)	63.0	-	
CYP2C9	63 (92.6)	32 (94.1)	31(91.2)	28.1 ± 11.0	4 (80)	0.17
*1/*1 (wild)	-	-	-	-	-	-
*1/*2	5 (7.4)	2 (5.9)	3 (8.8)	13.2 ± 1.1	1 (20)	0.78
*1/*3	-	-	-	-	-	-
*2/*2	-	-	-	-	-	-
*2/*3	-	-	-	-	-	-
*3/*3	-	-	-	-	-	-

In this study we prescribed the lower weekly warfarin dose about 27 mg which was less than Hylek's study (35.4 mg) and Kovacs' study (29.3 mg). The lower weekly warfarin dose may cause the shorter period to normalization of INR. In the three days group four cases had INR more than 1.5, one case had cirrhosis child B, one case had severe TR and two cases had no factors that may affect the warfarin dose. In the five days group one case with severe TR had INR more than 1.5. Severe TR and cirrhosis child B may affect slow metabolization and clearance of warfarin.

Prior studies showed VKORC1 and CYP2C9 influenced warfarin dose[3]. We hypothesized that the lower warfarin dose variants may required shorter periods of cessation of warfarin. From this pharmacogenetic study of warfarin in Thailand, the authors found quite similar prevalence of genetic variations of VKORC1 and CYP2C9 in this population compared to a Northern Thailand population. Neither mutant CYP2C9*2 allele nor homozygous CYP2C9*3 were found in the present study, which were reported to be higher in Caucasians by Takahashi and colleague[11,12] who demonstrated that the difference of warfarin clearance in genotype-matched patients has shown the significantly higher warfarin clearance of Japanese than Caucasian patients with homozygous CYP2C9*1. However, VKORC1 and CYP2C9 were not associated with normalization of INR in our study. Our population had lower warfarin dose and higher clearance, so the shorter time of normalization of INR. Since all of the patients in our study have mechanical valve implantation, the application can be used only in this population.

CONCLUSION

Temporary interruption of the warfarin therapy between three days and five days with bridging therapy before surgery is not significantly different in the Thai population. This study recommends discontinuing warfarin three days before surgery. The proper timing of interruption for warfarin not only depends on the half-life of warfarin, but also depends on age, sex, comorbidity, BMI, lower maintenance warfarin dose and concomitant drugs. If the patients had cardiac or liver disease, they may use longer time to discontinue warfarin before surgery.

REFERENCES

1. Douketis JD, Berger PB, Dunn AS, Jaffer AK, Spyropoulos AC, Becker RC, et al. The Perioperative Management of Antithrombotic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008 Jun;133(6 Suppl):299S-339S.
2. Schulman S, Elbazi R, Zondag M, O'Donnell M. Clinical factors influencing normalization of prothrombin time after stopping warfarin: a retrospective cohort study. Thromb J. 2008 Oct 16;6:15.
3. Wu AH. Use of genetic and non genetic factors in warfarin dosing algorithms. Pharmacogenomics. 2007 Jul;8(7):851-61.
4. Kuanprasert S, Dettrairat S, PalacajornsukP,Kunachiwa W, Phrommintikul A. Prevalence of CYP2C9 and VKORC1 Mutation in Patients with Valvular Heart Disease in Northern Thailand. J Med Assoc Thai. 2009 Dec;92(12): 1597-601.
5. Kovacs MJ, Kearon C, Rodger M, Anderson DR, Turpie AG, Bates SM, et al. Single-Arm Study of Bridging Therapy with Low-Molecular-Weight Heparin for Patients at Risk of Arterial Embolism Who Require Temporary Interruption of Warfarin. Circulation. 2004 Sep 21;110(12):1658-63.
6. Rose AJ, Ozonoff A, Berlowitz DR, Henault LE, Hylek EM. Warfarin dose management affects INR control. J Thromb Haemost. 2009 Jan;7 (1):94-101.
7. Boonbaichaiyapruck S, Panchavinnin P, Suthichaiyakul T, et al. Behavior of Prothrombin Time (INR) in Response to Warfarin Therapy in a Thai Population. Thai Heart J. 2006; 19(3): 85-89.
8. Douketis JD, Johnson JA, Turpie AG. Low-Molecular-Weight Heparin as Bridging Anticoagulation During Interruption of Warfarin Assessment of a Standardized Periprocedural Anticoagulation Regimen. Arch Intern Med. 2004 Jun 28;164(12):1319-26.
9. Ubonwan S. Impact of Physician-pharmacist Collaboration on The Management of Warfarin Therapy. A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science in pharmacy faculty of graduate studies Mahidol university 2006:109p.
10. Hylek EM, Regan S, Go AS, Hughes RA, Singer DE, Skates SJ. Clinical Predictors of Prolonged Delay in Return of the International Normalized Ratio to within the Therapeutic Range after Excessive Anticoagulation with Warfarin. Ann Intern Med. 2001 Sep 18;135(6):393-400.
11. Takahashi H, Kashima T, Nomoto S, Iwade K, Tainaka H, Shimizu T, et al. Comparisons betweenin-vitro and in-vivo metabolism of (S)-warfarin: catalytic activities of cDNA-expressed CYP2C9, its Leu359 variant and their mixture versus unbound clearance in patients with the corresponding CYP2C9 genotypes. Pharmacogenetics. 1998 Oct;8(5):365-73.
12. Takahashi H, Wilkinson GR, Caraco Y, Muszkat M, Kim RB, Kashima T, et al. Population differences in S-warfarin metabolism between CYP2C9 genotype-matched Caucasian and Japanese patients. Clin Pharmacol Ther. 2003 Mar;73(3):253-63.