Journal of Pharmaceutical Care
jpc.tums.ac.ir

International Normalized Ratio Response Subsequent to Modest Increase in Vitamin K Intake in Patients Treated with Warfarin

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Received:2015-10-12, Revised: 2015-11-13, Accept: 2015-12-19, Published: 2016-05-31

ARTICLE INFO

Article type:
Original article

Keywords:
Warfarin
International Normalized Ratio
Vegetables
Vitamin K
VKORC1

ABSTRACT

***Background*:** Warfarin is an effective oral anticoagulant which exert its effect by blocking the utilization of vitamin K. Warfarin therapy requires ongoing monitoring using the international normalized ratio (INR). In this study, effect of modest increase in vitamin K intake from vegetables on INR values was evaluated in warfarin treated patients.

***Methods*:** A single-center study involving 24 outpatients (mean age, 62 years) with two last INR in therapeutic range in which INR variations was less than 0.5. Patients were selected based on their *VKORC1* 1639G→A polymorphism so that 8 patients from each of GG, AA or GA genotypes were recruited. Patients were asked to consume a vegetable mix (including lettuce, peeled cucumber and tomato) containing approximately 100 µg vitamin K (divided in two meals, lunch and dinner) daily for one week when INR response was measured.

***Results*:** Daily consumption of vegetable mix decreased patient's INR from 2.43±0.51 to 2.08± 0.46 ($P<0.001$). INR value had a significant decrease in each *VKORC1* genotypes (from 2.55± 0.55 to 2.21± 0.54 in GG, 2.35± 0.33 to 2.00± 0.25 in AA, and 2.39± 0.65 to 2.00± 0.25 in GA) but the values did not differ between genotypes.

***Conclusions*:** Daily increase in vegetable salad containing approximately 100 µg, decreased INR of patients. Therefore, avoiding variation in consumption of foods with even moderate content of vitamin K could help to prevent INR fluctuations in warfarin treated patients.

J Pharm Care 2015; 3(1-2):3-6.

► Please cite this paper as:
Foroughi M, Miri R, Assarzadegan F, Nasrollahzadeh J. International Normalized Ratio Response Subsequent to Modest Increase in Vitamin K Intake in Patients Treated with Warfarin. J Pharm Care 2015; 3(1-2): 3-6.

Introduction

Warfarin is a commonly prescribed oral anticoagulant despite the significant challenge which its use presents. An insufficient warfarin dose leads to a lack of antithrombotic effect, whereas over-anticoagulation is associated with elevated bleeding risk (1). Vitamin K is an essential co-factor for the normal production of some key clotting factors. Warfarin reduces the regeneration of vitamin K from vitamin K epoxide by inhibiting the reductase enzymes in the vitamin K cycle. Patients taking warfarin are rendered deficient in regenerated vitamin K, and clotting factor synthesis is therefore likely to be critically

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dependent on oral intake of the vitamin. Therefore, vitamin K-rich vegetables are considered a major dietary factor contributing to the unstable effect of warfarin (2). In addition, several genetic polymorphisms are associated with warfarin dose requirements. Among the most studied genetic determinants of warfarin response is the polymorphisms in gene that encode the vitamin K epoxide reductase complex subunit 1 (*VKORC1*) (3). Common genetic variants of *VKORC*, such as the functional promoter SNP −1639G > A (rs9923231), results in enhanced warfarin sensitivity.

Previous clinical studies have examined the effects of vitamin K intake on INR in patients on anticoagulation medication and increase in vitamin K as much as 100 µg, have not had significant effect on INR in these patients (4, 5). Based on these researches, in this pilot study, we put forward two main hypotheses: first, in patients treated with warfarin, increased consumption of vegetables containing 100 µg/day vitamin K will not have a significant impact upon the INR response; and second, genetic variation in VKORC1 will influence the INR response of change in vitamin K intake.

Methods

Patients were recruited from the Imam Hussein hospital clinics. Inclusion criteria included patients anticoagulated with warfarin for thromboembolic prophylaxis who had been taking warfarin for at least 3 months and their last two measures of coagulation (taken as INRs) were in their therapeutic range with INR variations less than 0.5. *VKORC1* 1639G→A polymorphism of patients were determined using polymerase chain reaction and restriction fragment length polymorphism (6). Ethical approval for the study was obtained from the National Nutrition and Food Technology Research Institute, Shahid Beheshti University of Medical Sciences Ethics Committee. All participants gave fully informed written consent. An overnight-fasted venous blood sample was taken at study entry (day 0) and 1 week after increase in consumption of vegetables for the measurement of INR.

Patients were asked to consume a vegetable mix which is customarily eaten as a side dishes and consisted of fresh lettuce, peeled cucumber and tomato, plus one tea-spoon of olive oil, containing 100 µg vitamin K on a daily basis for one week. Patients were excluded if they did not consume vegetable mix during all days of the week. The amount of the vegetables that should be consumed by patients was instructed using standard household utensils. Total amount was divided to two equal parts and consumed along with lunch and dinner. Since tomato or peeled cucumber naturally have low levels of vitamin K, mainstay of increase in vitamin K intake was from lettuce which have comparable vitamin K bioavailability to fresh broccoli (7). Patients were asked not to change their usual diet during the study.

For comparisons of baseline with post vegetables consumption INR values, Wilcoxon signed ranks test was performed. Kruskal Wallis was used to demonstrate changes INR in VKORC1 genotypes. Differences were considered to be statistically significant at P less than 0.05. All statistical analyses were performed using SPSS 20.0 for windows (SPSS Inc., Chicago, IL, USA).

Results

Twenty four patients completed the study (Table 1). Eight patients were selected for each genotypes of GG, AA and GA. After one week vegetable mix consumption, INR values decreased from 2.43±0.51 to 2.08± 0.46 (mean difference 0.35; $P < 0.001$). INR response between the three genotypes were not significantly different from each other after one week of vegetables consumption (Table 2).

Discussion

In current study, an increase in daily consumption of a vegetable mix decreased INR of stably anticoagulated patients by 0.35. However, INR of most patients still remained in therapeutic range. The impact of increase in vitamin K intake on the anticoagulant effect of warfarin have been investigated in a few studies. Franco et al., put 12 patients, in a randomized crossover protocol, either on a 500% increased vitamin K intake or on an 80% decreased vitamin K intake relative to the baseline level (8). Both vitamin K enriched and vitamin K depleted diets affected INR stability. In a study by Schurgers et al., in healthy volunteers who had been stably anticoagulated with warfarin, the response to weekly incremental doses (50 -500 µg) of vitamin K1 supplements (K1) taken daily for 7 days was studied (5). As the dose of vitamin K increased, INR values decreased dose dependently. When the vitamin K supplement dose had reached 150 µg, the change in INR from baseline became statistically significant, while 100 µg supplement did not change INR significantly.

The result of current study is in contrast to Khan et al., (4) that reported for each 100 µg increase in vitamin K dietary intake over 4 days, the INR was reduced only by 0.2 or Schurgers et al., that showed additional 100 µg/day vitamin K1 supplement for one week non-significantly decreased INR values by 0.27 (5). Since vitamin K from food sources is less bioavailable when compared with that of the vitamin supplement, we had expected milder decrease in INR by intake of 100 µg vitamin K from vegetables. The reason for this discrepancy is unclear. Patients on warfarin are routinely instructed to restrict dietary source with relatively high vitamin K content in an attempt to achieve optimal therapeutic response. Although we did not evaluate previous vitamin K status of patients, they may have been vitamin K depleted and in vitamin K depleted patients, small changes in intake may be an

Table 1. Patients characteristic.

Characteristic	
Age (year) (Mean ± SD)	62 ± 16
Weight (kg) (Mean ± SD)	72 ± 10.5
Body mass index (Mean ± SD)	27.4 ± 3.7
Warfarin dose (mg/day) (Mean ± SD)	3.74 ± 1.05
Pre-enrollment INR (Mean ± SD)	2.50 ± 0.55
Indications for warfarin use (n)	
Atrial fibrillation	8
Valve replacement	5
Stroke	3
Deep vein thrombosis, pulmonary embolism	2
Other	7

INR, international normalized ratio

Table 2. Warfarin dose and change in INR after 7 days of increase in dietary vitamin K intake according to VKORC1 genotype.

	GG (n=8)	GA (n=8)	AA (n=8)
Warfarin dose at stable anticoagulation, mg	3.96 ± 1.32	3.79 ± 1.11	3.30 ± 1.04
INR before vegetable consumption	2.55 ± 0.55	2.39 ± 0.65	2.35 ± 0.33
INR after vegetable consumption	2.21 ± 0.54	2.03 ± 0.56	2.00 ± 0.25
Change in INR after vegetable consumption	-0.34 ± 0.16	- 0.36 + 0.18	- 0.35 ± 0.16
P value	0.012	0.012	0.011

INR, international normalized ratio

important determinant of anticoagulation response (9).

Kim et al., reported that stability of anticoagulant effect increased as dietary intake of vitamin K increased (10). They estimated average daily vitamin K intake based on a three-day food diary in patients taking warfarin regularly divided them into three groups of equal number according to vitamin K intake. Stability of anticoagulant effect was compared in these groups using the coefficient of variation of INR. High vitamin K intake (>195.7 µg/day) group had lower coefficient of variation of INR than the low intake (<126.5 µg/day) group. Their finding suggests that, with the large reservoir of daily vitamin K intake, a certain amount of change in vitamin K intake does not significantly affect the anticoagulant effect of warfarin. Lubetsky et al., studied correlation between vitamin K intake and warfarin sensitivity in patients consuming their regular diets (11). They found that sensitivity to warfarin is decreased by vitamin K intake ≥250 µg/day. Sconce et al., reported improvement of stability of anticoagulation by vitamin K supplementation (150 µg/day) in patients with unexplained variability in response to warfarin (12).

Other potential reason and a limitation of this study is that patients were asked to prepare and consume the vegetables themselves using household utensil. Compared to weighing method used by Khan et al., this may have caused measurement error in the amount consumed and actually patient have consumed more than a pre specified amount with more vitamin K intake than 100 µg.

The result of this study are partly consistent with results of Couris et al., that determined impact of variability in vitamin K intake on weekly INR in patients receiving warfarin (13). Participants recorded daily intake of foods by a dietary self-assessment tool in five weeks study periods. Variability in INR and changes in vitamin K intake were inversely correlated. The results of regression analysis indicated that an increase in dietary vitamin K of 714 µg over 7 days significantly associated with a decrease in INR of 1.0. This may imply that daily increase of 102 µg dietary vitamin K intake for one week could cumulatively decrease INR.

VKORC1 polymorphism influence warfarin dose requirements. However neither warfarin dose nor INR response were not significantly different between the three genotypes. This result is in contrast to Sconce et al., that reported a significantly larger decrease in INR of those patients carrying the GG genotype than those carrying the GA and AA genotypes following daily supplementation of 150 µg vitamin K (14). This is possibly because of other

genetic confounders, including *CYP2C9* polymorphism, which may influence INR response and/or a small sample size of current study.

The results obtained are potentially influenced by limited sample size that makes it difficult to extend the findings to the whole anticoagulated patients. However, avoiding variation in consumption of foods with even moderate content of vitamin K may help to prevent INR fluctuations in warfarin treated patients.

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