

Blood Coagulation, Fibrinolysis and Cellular Haemostasis

Patients with unstable control have a poorer dietary intake of vitamin K compared to patients with stable control of anticoagulation

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Summary

Evidence suggests that alterations in the dietary intake of vitamin K can affect anticoagulation response to warfarin. It is possible that a low and erratic intake of dietary vitamin K is at least partly responsible for the variable response to warfarin in patients with unstable control of anticoagulation. Twenty-six patients with unstable and twenty-six with stable control of anticoagulation completed dietary records of all foods and drinks consumed on a daily basis for two consecutive weeks. The mean daily intake of vitamin K in unstable patients was considerably lower than that for stable patients during the study period

($29 \pm 17 \mu\text{g}$ v. $76 \pm 40 \mu\text{g}$). The logarithm of vitamin K intake was consistently and significantly lower in the unstable patients than the stable patients over the two week period ($5.9 \pm 0.4 \mu\text{g}$ v. $6.9 \pm 0.5 \mu\text{g}$; $p < 0.001$; 95% CI: 0.7–1.2). Changes in vitamin K intake between weeks 1 and 2 of the study were negatively correlated with changes in International Normalised Ratio (INR) amongst the unstable patients, however this failed to reach significance ($r = -0.25$; $p = 0.22$). Daily supplementation with oral vitamin K in unstable patients could lead to a more stable anticoagulation response to warfarin.

Keywords

Warfarin, anticoagulation, diet, vitamin K

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Introduction

It is estimated that patients on chronic warfarin therapy are on average within their target range for only two-thirds of the time (1, 2). As a consequence, they are at risk of haemorrhage and thromboembolism, resulting from over- and under- anticoagulation, respectively (3, 4). Although several factors including age, concurrent medication, co-morbidity and compliance are known to affect anticoagulation in a predictable way, at present a large part of intra-individual variation in warfarin response cannot be explained.

Vitamin K is an essential co-factor for the production of functional clotting factors II, VII, IX and X, as well as the proteins C, S and Z (5). Warfarin exerts its anticoagulant effect by reducing the regeneration of vitamin K from vitamin K epoxide in the vitamin K cycle (6). Vitamin K is primarily obtained from the diet as phyloquinone (vitamin K₁), the highest concentrations of which are found in dark green leafy vegetables, with significant amounts also present in a number of fats and oils (7).

There is however little storage of vitamin K in the body (8). In patients taking warfarin, because of the reduced regeneration of vitamin K, the production of the functional vitamin K dependent clotting factors and proteins is therefore likely to be highly dependent on their oral intake of the vitamin.

To date there are no published data providing information about the relation of dietary intake of vitamin K to anticoagulation response to warfarin in patients with unstable control of anticoagulation. We hypothesised that a low and inconsistent intake of dietary vitamin K contributes to intra-individual variability in anticoagulation response, with those with unstable control of anticoagulation having a lower or more variable intake than those with stable control. We also hypothesised that variability in dietary intake of fat could affect patient anticoagulation consequent to its effect on vitamin K absorption. This study thus evaluated dietary intake of vitamin K and fat and their relation to anticoagulation response to warfarin in unstable patients compared to those with stable control of anticoagulation.

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Methods

Ethical Approval was obtained from the Joint University of Newcastle and Health Authority Ethics Committee. Patients were recruited from the anticoagulation clinics at the Freeman Hospital and Royal Victoria Infirmary, Newcastle-upon-Tyne. All participating patients were fully informed and written consent was obtained prior to the study.

Patient selection

Patients anticoagulated with warfarin whose target INR range was 2–3 were eligible to take part in the study. A patient was classified as unstable if the standard deviation of his/her INR values was >0.5 and had at least three dose changes during the previous six months. Those patients whose instability was thought to be due to poor compliance, concurrent medication, illness or irregular and excessive alcohol consumption were excluded from the study. Stable patients were defined as those having a standard deviation of INR values <0.5 and no change in warfarin dose during the previous six month period. Data for stable patients who matched the unstable group for age, sex and indication for warfarin therapy, were already available from a previous study (9).

Dietary method

Each patient was provided with two 7-day weighed intake food diaries, a food scale (Selectronic 2200, Salter, UK) accurate to 2 g, and the same set of detailed instructions on how to complete the food diaries in order to maximise the consistency and accuracy of dietary recording. Food and drink intakes were both measured by the cumulative method and leftover food was similarly weighed and recorded (10). For composite dishes, the portion eaten was weighed and a detailed list of the raw ingredients was also weighed and recorded. A number of previously validated photographs of commonly eaten foods e.g. potatoes, rice, cake etc. were included with the diary and used to estimate portion sizes when weighing was not possible, for example when eating out.

At the end of each week the patients were seen at the clinic, where dietary recall approaches were used when incomplete descriptions of food were reported (11). If a patient was unable to give details about either the weight or portion size then the weight of food eaten was approximated using average portion sizes (12).

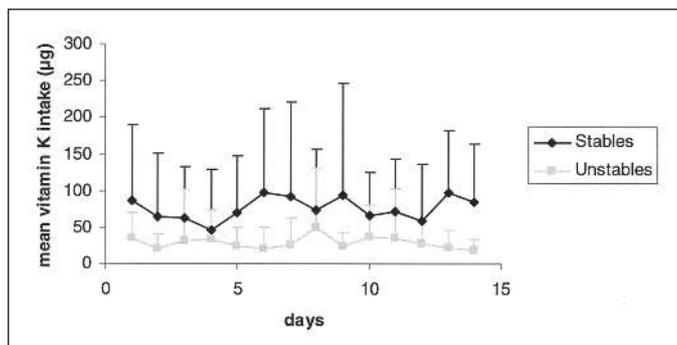


Figure 1: Mean +SD of Vitamin K intake for patients with unstable and stable control of anticoagulation over the two week study period.

Dietary analyses

The data were analysed using the computerised program, Microdiet (University of Salford), containing the 5th edition McCance & Widdowson Composition of Foods (13), plus Royal Society of Chemistry supplements 2–11 for the composition of foods. Dietary vitamin K and fat were quantitated using the above programme.

Statistical analysis

Minitab (version 13.1) was used to carry out statistical analysis of the data. Due to the skewed distribution of data for vitamin K intake the logarithm values were used for comparing stable with unstable patients. Two-sample t-tests were carried out to compare the mean intakes of both fat and vitamin K of stable and unstable patients. Standard deviation (SD) of vitamin K intake and variation about the mean was used as a measure of variability of intake. Pearson's correlation test was also performed to identify whether there was a relationship between changes in vitamin K intake and changes in INR as well as between fat and vitamin K intake. Results are presented as mean \pm SD unless otherwise stated. A p value of <0.05 was taken as statistically significant.

Results

Thirty patients with unstable control of anticoagulation consented to take part in the study. Of these, three patients failed to complete it; two patients (female) found it too tedious to complete the diaries and one patient (male) was admitted as an in-patient two days after commencing the study (unrelated to warfarin therapy). On completion of the diaries one patient (male) was found to have an excessive and irregular intake of alcohol. As this was a potential cause for his instability, the data from this patient were excluded from final analysis. Twenty six patients were therefore included in the statistical analysis. For comparison, data from the same number of patients with stable control of anticoagulation matching the unstable patients were used. Demographic details of the unstable and stable patients are given in Table 1.

Comparison of vitamin K intake between stable and unstable patients

The mean daily intake for unstable patients was considerably lower than that for stable patients ($29 \pm 17 \mu\text{g}$ v. $76 \pm 40 \mu\text{g}$) (Fig. 1). The logarithm of vitamin K intake was consistently and significantly lower in the unstable patients than that in the stable patients over the two week period ($5.9 \pm 0.4 \mu\text{g}$ v. $6.9 \pm 0.5 \mu\text{g}$; $p < 0.001$; 95% CI: 0.7–1.2). The logarithm of intake did not significantly differ between the two weeks of the study for both the

Table 1: Demographics of patients with unstable and stable control of anticoagulation.

Variable	Unstable Patients	Stable Patients
Median Age (range) (years)	71 (27–84)	70.5 (24–81)
Sex	11 males; 15 females	11 males; 15 females
Primary Indication for warfarin therapy	22– Atrial Fibrillation 4– Deep Vein Thrombosis	21– Atrial Fibrillation 5– Deep Vein Thrombosis

unstable (5.1 ± 0.5 v. 5.2 ± 0.6 ; 95% CI: -0.4 – 0.2) and stable patients (6.0 ± 0.7 v. 6.2 ± 0.6 ; 95% CI: -0.5 – 0.2). Gender had no significant effect on mean logarithm of vitamin K intake ($3.7 \pm 0.7\mu\text{g}$; females, $3.9 \pm 0.7\mu\text{g}$; males; $p=0.32$). The logarithm of the SD of intake over the two weeks was significantly lower amongst the unstable patients than the stable patients ($3.4 \pm 0.6\mu\text{g}$ v. $4.2 \pm 0.6\mu\text{g}$; $p<0.001$; 95% CI: 0.5 – 1.2).

Relationship between vitamin K intake and INR

Simple correlation of changes in vitamin K intake between week 1 and 2 of the study and changes in INR in unstable patients showed a weak negative correlation, however this failed to reach significance ($r=-0.25$; $p=0.22$).

Comparison of fat intake between stable and unstable patients

Although mean fat intake over the two weeks was higher in the stable patients than the unstable patients the difference did not reach significance ($66 \pm 24\text{g}$ v. $56 \pm 11\text{g}$; $p=0.06$; 95% CI: -0.3 – 21).

Relationship between fat and vitamin K intake

Simple correlation analysis of the data showed no significant correlations between fat and vitamin K intake amongst the stable patients ($r=0.075$; $p=0.72$) or the unstable patients ($r=-0.178$; $p=0.38$).

Discussion

A number of case reports and experimental studies have described the impact of dietary intake of vitamin K on anticoagulation response to warfarin (14–20). Recently it was reported that the administration of oral vitamin K doses of 150 – $500\mu\text{g}/\text{day}$ for 7 days caused significant reductions in INR in healthy subjects receiving acenocoumarol and with stable control of anticoagulation (21). We have demonstrated that, in patients with stable control of anticoagulation for every 100 microgram increase in dietary vitamin K intake over the previous 4 days INR value fell by 0.2 (9), further clarifying the extent of the inter-relationship between dietary vitamin K and the INR. To date however there are no published reports on the impact of dietary vitamin K on response to warfarin in patients with unstable control of anticoagulation. The benefit of dietary vitamin K monitoring and its role in the management of oral anticoagulation therapy therefore still remains unclear.

The results of the present study demonstrate that patients with unpredictable and unstable anticoagulant response to warfarin consume significantly lower amounts of vitamin K than do their matched stable counterparts; the average intake for stable patients was 261% higher than for the unstable patients. The mean intake of vitamin K has been estimated at around 60 – $80\mu\text{g}$ per day in the UK, with individuals over the age of 85 years generally consuming lesser amounts than younger subjects (22). In our two cohorts of patients, however, no significant correlation was found between patient age and mean vitamin K intake. The average daily intake of vitamin K for unstable patients was less than half the dietary reference value of 65 – $80\mu\text{g}/\text{day}$, with only one patient in this group consistently consuming greater than

$65\mu\text{g}/\text{day}$. On the other hand, the average daily intake of vitamin K for stable patients was either within or higher than the dietary reference range, with only three stable patients falling short of this value.

Both the groups had a highly variable intake of vitamin K. This is because vitamin K is found in high quantities in only a limited number of foodstuffs and people may not consume these on a daily basis (23). Variability of intake, as measured by the standard deviation (SD), was significantly higher in the stable patients, compared to the unstable patients. Since SD is based on variance around the mean (with mean vitamin K intake being greater in stable patients than unstable patients) the values for the two groups can not be directly compared. The variable vitamin K intake in stable patients did not affect their stability of anticoagulation, likely due to their consistently high intake and thus a greater body store of phyloquinones for steady clotting factor activation. Conversely, in unstable patients because of their consistently lower vitamin K intake body stores of the vitamin could be depleted more rapidly. This renders them vulnerable to even small changes in dietary intakes of vitamin K, which translate at the physiological level into large variations in production of active clotting factors, particularly those with short half-lives, for example factor VII (24).

The results also showed the presence of an inverse relationship between changes in vitamin K intake and changes in INR amongst the unstable patients, but this failed to reach significance, possibly due to a relatively small sample size and short study period.

Dietary fat could also affect anticoagulation response to warfarin through its effect on vitamin K absorption. It is estimated that a meal containing over 35 grams of fat maximises vitamin K oral bioavailability (25). In both the cohorts mean daily fat intake far exceeded this value. Moreover, there was no significant difference in fat intake between the two groups. These suggest that variable dietary fat intake was not a confounding factor in the unstable patients.

Patients in the stable and unstable groups were matched according to age, sex and primary reason for anticoagulation and therefore these factors were not responsible for the differences in anticoagulation control between the two groups. This study also assessed patients who had been taking warfarin for at least six months, thus removing the variability in anticoagulation response consistently seen at the onset of treatment.

Because of the broad range in the mean vitamin K intake for the stable patients which overlapped with that in unstable patients, it would not be feasible to ascertain stability of anticoagulation control in a patient solely based on his/her vitamin K intake. Nevertheless, the findings from the present study indicate that adequate intake of vitamin K could improve the stability of anticoagulation control. With food composition data for vitamin K now available, the design of menus to help provide a more consistent dietary intake of vitamin K has been advocated (7, 26). However such recommendations could be difficult for both patients and their carers to implement (23).

Daily supplementation with vitamin K could be an alternative method in stabilising anticoagulation control, lessening the impact of variable dietary vitamin K intake. We are currently evaluating this possibility.

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