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WARFARIN THERAPY, VITAMIN K AND OTHER DIETARY FACTORS

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INTRODUCTION

Warfarin (Coumadin and Marevan) is an extensively used anticoagulant drug used for treatment and prophylaxis of thromboembolic events in conditions such as atrial fibrillation, deep vein thrombosis, pulmonary embolism, embolic stroke and prosthetic valve replacement. Its mechanism of action involves the inhibition of clotting factors II, VII, IX and X, and proteins C and S, which are dependent on vitamin K for activation.

Despite its great therapeutic value, it is a difficult drug to manage and stabilize, because of its narrow therapeutic range, the variable responsiveness of patients and its propensity to interact with many other drugs and foods. Such instability can lead to ‘therapeutic failure’, resulting in either thromboembolism, or bleeding complications. Doctors need to regularly monitor patients, using an index called the International Normalised Ratio (INR), based on prothrombin time, reflecting the amount of time it takes for blood to clot.

Doctors and other health professionals need to inform patients of potential interactions, and dietitians are often in a position where they may detect risky dietary or supplementation practices.

Please note that there may be more than one correct answer to some questions.

1. What is the usual target therapeutic INR level?
   a. 1.0–2.0
   b. 2.0–3.0
   c. 3.0–4.0
   d. 4.0–5.0

2. Which answer correctly describes the effect of a high intake of vitamin K on warfarin therapy?
   a. It will decrease the effect of warfarin, thereby raising INR
   b. It will decrease the effect of warfarin, thereby lowering the INR
   c. It will enhance the effect of warfarin, thereby raising the INR
   d. It will enhance the effect of warfarin, thereby lowering the INR

3. What should people who take warfarin be advised regarding foods rich in vitamin K?
   a. Don’t worry about the vitamin K content of foods, as the dose is insignificant
   b. Avoid foods high in vitamin K
   c. Consume a constant amount of vitamin K every day, consistent with the AI
   d. Increase warfarin dose on days when you choose to eat more vitamin K-rich foods

4. Which of the following foods are high in vitamin K?
   a. Spinach, broccoli, cabbage and some lettuces
   b. Green beans, peas, green capsicum and celery
   c. Carrots, potatoes and cauliflower
   d. Green grapes, green apples and kiwifruit
   e. Meat, eggs and milk

5. Apart from the function of vitamin K in activating clotting factors, what other important function does vitamin K perform?
   a. Improves insulin sensitivity
   b. Cofactor for energy production in mitochondria
   c. Assists immune function
   d. Assists bone mineralization

6. In addition to interactions between warfarin and vitamin K, there have been several case reports indicating possible interactions with other specific foods, including which of the following?
   a. Grapefruit and grapefruit juice
   b. Cranberry juice
   c. Avocado
   d. Mango
   e. Alcohol
   f. All of the above

7. Which of the following dietary practices may be associated with a significant change in INR?
   a. Fasting for several days
   b. Replacing high-GI foods with low-GI alternatives of the same food category
   c. Starting a high-protein, low-carbohydrate weight loss diet
   d. Enteral feeding
   e. All of the above

8. Which of the following statements is/are correct regarding the use of nutrient supplements?
   a. All multivitamin supplements should be avoided
   b. Nutrient supplement drinks, such as Fortisip, Resource and Sustagen, contain vitamin K and should be avoided
3. c. Mega-dose supplementation with vitamins A, C and E is not advisable
d. Mineral supplements, such as iron, zinc and magnesium, can increase INR
e. Fish oil supplements increase risk of bleeding episodes and should be avoided
f. Many herbs affect blood clotting, so medical advice should be sought before taking any herbal supplements
g. All of the above

ANSWERS

1. b.
The usual INR target for most applications, such as prophylaxis against myocardial infarction, is 2–3. However, there are some applications, such as treatment of patients who have prosthetic heart valves, where the target level may be a little higher (e.g. 2.5–3.5). A lower INR level, such as less than 2, indicates inadequate warfarin therapy, and an increased risk of thrombosis. An INR higher than 3.0 indicates a greater risk of bleeding events.

2. b.
Warfarin decreases the ability of blood to clot by interrupting the normal metabolism of vitamin K in the liver. The reduced form of vitamin K is an essential cofactor for the conversion of glutamic acid to γ-carboxyglutamic acid residues in six proteins that promote blood clotting—factors II, VII, IX, X and proteins C and S. These γ-carboxyglutamic acid residues bind calcium, which mediates the binding of the proteins to membrane phospholipids at the site of vascular injury. During the γ-glutamyl carboxylation process, the reduced form of vitamin K is oxidised to an inactive form, and it is normally regenerated in a redox reaction, partially by the enzyme vitamin K 2,3-epoxide reductase. Warfarin inhibits vitamin K 2,3-epoxide reductase, thereby depleting active vitamin K, resulting in more under-carboxylated clotting proteins with lower biological activity. Exogenous vitamin K can replenish depleted stores of reduced vitamin K, and overcome the warfarin-associated disruption of carboxylation. A sufficiently high dose of vitamin K will completely reverse the effect of warfarin, with doses of 1–10 mg/day being used therapeutically to reverse the effects of warfarin in situations of over-anticoagulation.

3. c.
Unlike other fat-soluble vitamins, vitamin K is not stored in the body, and blood levels fluctuate according to recent dietary intake. There is strong evidence that the interaction between dietary vitamin K and warfarin is clinically relevant, and plays a major role in fluctuations in INR. Exactly how much change in dietary vitamin K intake is required to cause clinically significant effects, however, still remains unclear. The authors of a recent review refer to findings that dietary vitamin K intake over 250 μg/day decreased warfarin sensitivity, and that for each 100-μg increase in vitamin K, the INR decreased by 0.2. The usual recommendation given by authorities is to suggest a regular daily intake of vitamin K, in an amount consistent with the average daily intake of the population. The current AI for Australian adults is 60–70 μg/day, based on the 1995 National Nutrition Survey of Australia. Patients on warfarin have their INR regularly monitored, so the therapeutic dose can be adjusted to a normal modest dietary intake. There is no need to totally avoid vitamin K-rich foods, as some patients believe, but care needs to be taken with serving sizes and consistency of intake. There is some evidence, in fact, to suggest that patients who have a very low vitamin K intake, and therefore low body stores, are at more risk of unstable INRs, as they are more vulnerable to even small changes in dietary vitamin K intake.

Some individuals in the community have been reported to have intakes of vitamin K as high as 600 μg to over 2000 μg/day. These higher levels are in the range of doses (1–10 mg/day) used pharmacologically to reverse the effects of warfarin, although the absorption rate of vitamin K from food is 3–20 times less than that from supplemental forms. A 700-μg dose of vitamin K from broccoli, for example, is equivalent to approximately 200 μg of the supplemental form.

4. a.
Vitamin K mainly occurs in dark green vegetables. The main form of vitamin K found in foods is phyloquinone (vitamin K1). Some vitamin K is produced by endogenous gut bacteria, in the form of menaquinones (vitamin K2), although less is known about their contribution to human nutrition. The phyloquinone content of plant leaves is strongly related to the chlorophyll content, so a general rule is that the greener the plant, the higher the phyloquinone content.

Very dark green leafy vegetables have vitamin K levels of 80–500 μg per 1/2 cup cooked serve. Kale, collards and spinach have levels of approximately 500 μg per serve. Broccoli, brussels sprouts and cabbage are between 80–150 μg per serve. One cup of dark green lettuce varieties contains about 100 μg. Peas, beans, green capsicum and celery are relatively low at less than 30 μg per 1/2 cup, as are root vegetables, cauliflower and other non-green vegetables. Breads and cereal grains, nuts, fruits, meat, fish, eggs and dairy products contain low levels of vitamin K. Fats and oils are generally low in vitamin K, although adding fat to a meal promotes vitamin K absorption. A lesser-known but very rich source of vitamin K is natto, a traditional fermented soybean food, produced by growing Bacillus natto on the surface of cooked soybeans.
6. f.

Much of the evidence for food–warfarin interactions is derived from case reports, with limitations, such as publication bias, lack of controlled conditions and potential confounding factors. Nonetheless, these reports may help identify adverse interactions that could otherwise be overlooked and alert practitioners to potential idiosyncratic responses in some patients. The few reports from small experimental studies have not always supported the case reports, and deciding which interactions are worth mentioning to patients is a matter of educated opinion. There is one documented case report of an increased INR in a patient who drank 1.5 L of grapefruit juice per day, but a small clinical trial, in which nine warfarin-treated men consumed 750 mL/day of grapefruit juice for one week, showed no significant change in INR.\(^14\) Grapefruit juice is known to interact with some drugs because unique grapefruit bioflavonoids inhibit cytochrome P450 enzymes, CYP1A2 and CYP3A4.\(^14\) The most potent form of warfarin, the (S)-enantiomer, is metabolised by a different enzyme, CYP2C9, although the less potent (R)-enantiomer is metabolised by CYP1A2 and CYP3A4. Data on interactions between warfarin and grapefruit juice are sparse, and routinely warning patients is probably unwarranted.

Cranberry juice is frequently used to prevent and treat urinary tract infections. There have been several case reports of interactions between high doses of cranberry juice and warfarin, with bleeding episodes caused by a marked increase in INR. At least 12 interactions had been reported to the United Kingdom’s Committee on Safety of Medicines as of October 2004,\(^13\) with more case reports in the literature since then. The committee advised patients taking warfarin to avoid cranberry products if possible, or to be closely monitored during concurrent use. However, small clinical trials have not furnished supportive evidence, at least for small quantities of cranberry juice up to 250 mL/day.\(^15\)-\(^17\) The authors of one review article conclude that the evidence in total warrants cautioning patients taking warfarin about the potential for significant clinical interactions with large amounts of cranberry juice, and to consume it in moderation.\(^15\)

There have been two reported cases of interactions between warfarin and avocado.\(^18\) Consumption of 100–200 gm avocado per day was linked with a significant decrease in INR in a 15-year-old girl and a 30-year-old pregnant woman in Israel, and in both cases, INR returned to normal when avocado was ceased. Avocado is low in vitamin K, and the exact mechanism for the observed effect in these case reports is unknown. Given the paucity of other such reports, it is unlikely to be of significant concern to most warfarin users.

An average increase in INR of 38% was reported in 13 male patients who had started eating between one and six mangos per day, with no other dietary or medication changes.\(^19\) When mango consumption ceased, the average INR fell by 17.7%. The author of this report postulated that a possible mechanism was the high level of vitamin A (8000 IU per medium mango) inhibiting the cytochrome P450 enzyme that metabolises warfarin. Many studies have confirmed that modest intakes of one to three serves of wine or beer will generally not have a significant effect on the INR in healthy patients.\(^20,21\) However, in patients with liver impairment, or chronically heavy or binge drinkers, the effect is variable, depending on the amount consumed and presence of underlying liver disease. The half-life of warfarin may be lower in alcoholics, as a result of stimulation of liver enzymes that metabolise warfarin. On the other hand, alcohol may also change the ability of the liver to synthesise clotting factors. Patients should avoid chronic and excessive alcohol intake or binge drinking.

In addition to the interactions discussed above, there are theoretical concerns about licorice, which has demonstrated anti-platelet activity \textit{in vitro}, and seems to induce CYP2C9 metabolism of warfarin in animal models, thereby decreasing INR.\(^22\) There has also been one case report about an interaction with soy milk.\(^23\) No doubt more case reports of food and warfarin interactions will be documented as time goes on! A useful reference is the systematic review of warfarin and drug and food interactions published in 2005,\(^24\) summarised again in 2006.\(^25\) Given the possibility that individual patients may have idiosyncratic interactions between warfarin and a variety of foods, not all of which may have yet been reported in the literature, it is worth asking about any recent significant dietary changes when a previously stable patient experiences a significant change in INR for no other apparent reason.

7. a., c. and d.

Fasting will obviously reduce dietary vitamin K intake! In one study,\(^6\) reduction of vitamin K intake from 118 ± 51 \(\mu g\)/day to 26 ± 8 \(\mu g\)/day over four consecutive days resulted in a statistically significant increase in INR of almost 30%. It is unknown whether significantly reduced vitamin K intake for just one or two days will have a significant effect. Dietitians should be alert to the possibility of changes in INR in any warfarin-treated patient experiencing significantly reduced food intake. There have been no known reports that a low-GI diet \textit{per se} has affected INR. However, if people are taking warfarin and change their intake of dark green leafy vegetables as part of any new diet, it may have an effect on INR.

There have been three recent case reports of reduction in INR when people have commenced low-carbohydrate, high-protein diets for weight loss, despite no self-reported change in vitamin K intake.\(^26,27\) In these case reports, the warfarin dose needed to be increased by
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16–30% to return the INR to target, and the dose needed to be adjusted down again when the diet was ceased. An increase in warfarin metabolism because of cytochrome P450 activation is postulated to be the most likely cause. Studies in animals and humans have shown a relationship between protein intake and CYP enzyme activity. Although information on the potential interaction between warfarin and dietary protein is limited, it is a possibility worth noting, given the current popularity of high-protein diets for weight loss.

Before 1980, there were problems reported with enteral and parenteral feeds that contained high doses of vitamin K in the order of 960–1580 μg/L, but the industry responded by lowering the vitamin K content closer to a normal dietary intake. However, there continue to be case reports, supported by an in vitro study and a small retrospective case series, of warfarin resistance occurring with concurrent continuous enteral feeding. The mechanism appears to be the binding of warfarin by the protein component of the feed, reducing its bioavailability. In the case series, the effect did not occur if enteral feeding was withheld for one hour before and after warfarin administration.

8. f. and possibly c.

Not all multivitamin supplements contain vitamin K. Some, however, contain amounts approximating 50% of the AI (e.g. Cenovis Women’s Multi and Centrum Complete from A to Zinc each contain 36 μg per capsule/tablet). The form of vitamin K used in supplements is often a synthetic form called menadione (vitamin K3), and the absorption rate from supplements may be significantly higher than that from foods. Vitamin K may also be found in some other products, such as calcium supplements or ‘bone health’ formulations and sports bars, and the total daily dose for users of multiple supplements can become excessive. A prospective, controlled crossover trial demonstrated that multivitamin supplements containing 25–μg vitamin K1 significantly lowered INR, but mainly in patients with low plasma levels of vitamin K. Patients with normal plasma levels of vitamin K were much less likely to be affected. A systematic dose–response study in healthy volunteers indicated that the threshold dose of vitamin K supplementation that caused a statistically significant lowering of INR was 150 μg/day. A third group of investigators, which found that a group of patients with less stable control of INR had a lower daily intake of vitamin K compared with those with more stable control, suggested that daily supplementation with low-dose vitamin K may be worth evaluating as a strategy to lead to more stable anticoagulation! Perhaps the most prudent advice is to maintain a moderate, rather than low, dietary vitamin K intake, and to either avoid supplements containing vitamin K, or to otherwise maintain a consistent daily intake of supplemental vitamin K in very small doses only.

The dose of vitamin K in nutrient drink-type supplements, such as Fortisip, Resource and Sustagen, is in the range of 8 –20 μg per 200 mL, and these drinks are unlikely to have significant impact if used in small amounts (one to three cups per day) to supplement normal meals. In fact, they may even assist to maintain a more stable dietary vitamin K intake in patients who would otherwise have decreased vitamin K intake because they are not eating well.

The effects of mega doses of vitamins A, C and E are unclear. Vitamin E has been associated with increases in INR, although there is conflicting evidence in the literature. Some authorities recommend a limit of 400 IU of vitamin E per day, although others believe that amounts up to 1200 IU are safe, although perhaps not in all patient populations. Some case reports suggest that vitamin C might increase the activity of warfarin, but this has not been confirmed in research studies. In fact, although the interaction is uncertain and not proven, high-dose vitamin C may possibly reduce the effect of warfarin by reducing its absorption because of diarrhoea. Doses of less than 5 gm/day of vitamin C do not seem to be clinically significant. The Natural Medicines Data Base rates the potential interaction between warfarin and vitamin A as a possible occurrence, but with a level of evidence of ‘D’ (from pharmacological theory, anecdotal evidence or in vitro or animal studies). It advises avoiding doses of vitamin A above 10 000 IU/day. Mega-dose supplementation with B group vitamins has not been reported to have an adverse effect on INR. At this stage, the most prudent advice is to avoid taking mega-doses of vitamins A, C and E, or to closely monitor INR if a high-dose supplement is taken.

Mineral supplements do not raise INR. However, iron, magnesium and zinc may bind with warfarin, potentially decreasing its absorption and activity. People on warfarin therapy should take warfarin and iron/magnesium/zinc-containing products at least two hours apart. High-dose fish oil has many cardiovascular benefits, particularly its capacity to stabilize the myocardial membrane, thereby reducing ventricular fibrillation and sudden death, but also to improve blood pressure control, reduce fasting triglycerides, increase HDL cholesterol and improve arterial compliance and flow-mediated dilation. It also has anti-platelet effects. Due to its powerful anti-inflammatory effect, high-dose fish oil is also becoming increasingly popular as an effective treatment for arthritis, with a lower risk profile than most anti-inflammatory drugs. Arthritis occurs more frequently in the age group of patients who are also more likely to take warfarin, so many patients and doctors have concerns about potential risks of interactions. Within the context of the average Western diet, fish oil supplementation has not been associated with an increased frequency of bleeding events, even in patients taking aspirin or warfarin. The Natural Medicines Comprehensive Database lists the interaction rating as ‘minor’, but suggests monitoring INR more frequently initially when a patient starts taking fish oil. There are rare anecdotal reports of increased INR when fish oil supplementation is
Many herbal supplements can interact with warfarin, as do many medications. Some herbs alter the metabolism of warfarin by the cytochrome P450 enzymes. Others have effects on platelet aggregation, and some contain natural coumarins, although not all of these potential interactions have been documented in actual human case studies. Herbs that may increase clotting time include chamomile, daneshen, devil's claw, dong quai, fenugreek, feverfew, concentrated garlic and ginger extracts, gingo biloab, kelp and red clover. Herbs that may decrease clotting time include alfalfa, coenzyme Q10, ginseng, green tea and St John's Wort. It is worth noting that drugs and herbs that change clotting time do not necessarily show up as changes in INR. Given the wide range of interactions of warfarin with herbs and supplements, it is important for patients on warfarin to seek the advice of their doctor and notify them of any changes in supplement intake. Advice can also be sought from the National Prescribing Service.

The National Prescribing Service (http://www.nps.org.au) is a useful Australian website with information about a wide range of medicines. Health professionals can also call the Therapeutic Advice and Information Service, which is funded by the National Prescribing Service, on 1300 138 677. Its pharmacists have access to a database which is funded by the National Prescribing Service, on call the Therapeutic Advice and Information Service, and they have the ability to consult with the Therapeutic Issues and Information Service which is funded by the National Prescribing Service. Health professionals can also contact the National Prescribing Service Medicine Line on 1300 888 763.

REFERENCES

26. Beatty S, Mehta B, Rodis J. Decreased warfarin effect after commencement (L Cleland, personal communication, 2008). Other herbs that alter the metabolism of warfarin by the cytochrome P450 enzymes. Others have effects on platelet aggregation, and some contain natural coumarins, although not all of these potential interactions have been documented in actual human case studies. Herbs that may increase clotting time include chamomile, daneshen, devil’s claw, dong quai, fenugreek, feverfew, concentrated garlic and ginger extracts, gingo biloab, kelp and red clover. Herbs that may decrease clotting time include alfalfa, coenzyme Q10, ginseng, green tea and St John’s Wort. It is worth noting that drugs and herbs that change clotting time do not necessarily show up as changes in INR. Given the wide range of interactions of warfarin with herbs and supplements, it is important for patients on warfarin to seek the advice of their doctor and notify them of any changes in supplement intake. Advice can also be sought from the National Prescribing Service.

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33 Therapeutic Research Faculty. Natural Medicines Comprehensive Database. Stockton, CA: Therapeutic Research Faculty (reference accessed and provided by the National Prescribing Service on 20 Aug 2008.) Available from URL: http://www.naturaldatabase.com