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DIETARY IMPACT ON THE ANTICOAGULANT EFFICACY OF VITAMIN K ANTAGONISTS

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ABSTRACT

Background: The vitamin K antagonists' (VKA) mechanism of action is closely related to the metabolic pathways of vitamin K. Dietary vitamin K intake can directly translate into efficacy of VKA therapy.
Aim: The aim of the study was to summarize information about the role of vitamin K in the coagulation process and its impact on Vitamin K Antagonists.
Material and methods: A non-systematic litrerature review was conducted using databases such as Pubmed and Cochrane Database. Search terms included VKA pharmacokinetics, INR targets and dietary management strategies.
Results: Irregular intake of vitamin K negatively affects the action of hydroxycoumarin derivatives by causing INR fluctuations and subtherapeutic anticoagulation. Excessive doses of vitamin K reduce VKA activity and increase risk of side effects such as thromboembolic complications.
Conclusions: Effective anticoagulation with VKAs requires personalized dosage, regular INR monitoring and conscious management of vitamin K intake.

KEYWORDS

Oral Anticoagulants, Vitamin K, Vitamin K Antagonists, Warfarin, INR

CITATION

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Introduction

For over 80 years oral anticoagulants (OAC) have been used in treatment and prevention of thromboembolic events. The population of patients receiving OAC treatment increases every year due to the aging society and expanding indications. [1] First oral anticoagulant (OAC) was discovered by biochemist Karl Paul Link. In the 1930s, he was investigating a case of cattle epidemic, which occurred near his laboratory in Wisconsin. He discovered that fermented sweet clover (Melilotus spp.) contained a toxin, causing bleeding episodes. In 1939 Link et al identified this substance as a Vitamin K antagonist (VKA) - dicoumarol. The drug patent was granted by the Wisconsin Alumni Research Foundation (WARF), to which it owes the name - Warfarin. Later in the 1950s, warfarin became the second most important anticoagulant in clinical practice (after heparin). [2]

Although non-vitamin K oral anticoagulants (NOACs) are now the preferred form of anticoagulant treatment due to their safety profile, VKAs remain the standard treatment in patients with mechanical heart valves, vascular prostheses, and some cases of atrial fibrillation. [3]

Regarding their clinical relevance, it is important to understand the mechanisms affecting their pharmacokinetics and anticoagulant effect. One of the important factors influencing the efficacy of VKAs is diet - especially vitamin K intake. Vitamin K can significantly affect the pharmacological efficacy and therapeutic stability of VKAs. This article aims to examine dietary habits and their impact on patients receiving VKAs therapy.

Understanding vitamin K antagonists

Mechanism of the Vitamin K Antagonists

Vitamin K (KH2) plays a crucial role in the process of hemostasis by functioning as a cofactor for the post-translational γ-carboxylation of glutamate residues on coagulation proteins. The γ-carboxylation allows these proteins to bind calcium ions, which is critical for their interaction with phospholipid surfaces during the coagulation cascade. Vitamin K antagonists inhibit the γ-carboxylation of vitamin K-dependent clotting factors II, VII, IX and X.[4] VKAs block vitamin K epoxide reductase (VKOR), which catalyzes the conversion of quinone hydroperoxide to KH2. Its deficiency impairs the post-translational modification of vitamin K-dependent factors. As a result, the liver produces abnormal forms of the coagulation proteins - a protein induced by vitamin K absence (PIVKA) resulting in impaired coagulation and an increased risk of bleeding. [5] VKAs also inhibit carboxylation of the natural anticoagulant proteins C, S, which may be associated with the risk of thrombotic complications, especially in the first days of treatment, before the anticoagulant effect occurs.[6]

Commonly Prescribed Vitamin K antagonists

Currently, the most commonly used VKAs in clinical practice are warfarin, acenocoumarol and phenprocoumon. Although their mechanism of action is nearly identical, they differ in their pharmacokinetic features and bioavailability.

Warfarin is a racemic mixture of S-warfarin and R-warfarin. The first one is 2-5 times more potent than the R form in terms of anticoagulant activity. It is absorbed primarily in the stomach and proximal small intestine, with a high bioavailability (80-100%). Peak plasma concentration is typically achieved within 1-2 hours. The drug has a relatively long and variable elimination half-life of 20 to 60 hours and it is mostly metabolized in the liver mainly via the CYP2C9 enzyme. In case of excessive anticoagulation or bleeding, vitamin K administration is recommended to reverse the anticoagulant effect. [1]

Acenocoumarol also belongs to the family of VKAs and is used in France and Italy. The clinical activity of acenocoumarol is mainly dependent on R-acenocoumarol despite being the less potent isoform, due to its longer half-life. [7] It demonstrates high bioavailability and reaches peak plasma concentration within approximately 1 to 3 hours. [8] One of the key pharmacokinetic differences is its shorter elimination half-life, typically ranging from 8 to 11 hours, which may lead to more variable INR levels and necessitate more frequent dose adjustments.[9] Acenocoumarol is metabolized primarily in the liver via the CYP2C9 enzyme and its metabolites are excreted through both renal and biliary pathways. [10]

Phenprocoumon is a long-acting vitamin K antagonist widely used in parts of Europe, particularly Germany, the Netherlands, and Switzerland. [11] It is characterized by a rapid and nearly complete absorption from the gastrointestinal tract. Phenprocoumon has a longer elimination half-life than both warfarin and acenocoumarol, between 3 and 7 days, [12] which allows for once-daily dosing and potentially more stable INR levels over time. However, this also means that it may take longer to reverse its effect in emergency situations. The drug shows extensive plasma protein binding (approximately 99%) and a low volume of distribution, reflecting limited tissue penetration. Metabolism occurs in the liver via the CYP3A4 and CYP2C9 pathways. Inactive metabolites are excreted through both renal and biliary routes. Because of its prolonged half-life, phenprocoumon may be beneficial in patients with compliance problems or fluctuating INR levels. [13]

Despite the usefulness of VKAs in daily practice, there are limitations. One is a narrow therapeutic index, which results in frequent INR monitoring to avoid hemorrhagic complications. Depending on the clinical indications and the age of the patient, the therapeutic INR may be slightly different, it is mostly in the range of 2.0-3.0. [14]

Genetic polymorphism of CYP2C9 play a major role in pharmacokinetic of the VKAs, accounting for up to 15-40 % of the variance in warfarin dose requirements.

Patients who carry alleles of the CYP2C9 gene, particularly CYP2C92* or CYP2C93*, show slower metabolism of warfins' stronger S-enantiomer. As a result, warfarin accumulates in the bloodstream, requiring lower doses to avoid haemorrhagic complications. [15]

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Importance of Vitamin K

Vitamin K is a fat-soluble substance that naturally occurs in two forms - vitamin K1 (phylloquinone) and vitamin K2 (menaquinone). Vitamin K3 (menadione), a synthetic form, is not naturally occurring and is considered a provitamin. Vitamin K1 is synthesized exclusively in plants and taken in with food, while K2 is a group of compounds known as menaquinones (MK-n) synthesized by bacteria in the gastrointestinal tract. They are mainly found in animal-derived products including fermented ones. Vitamin K is stored in the liver, approximately 1.5 µg/kg. [16] The intake of vitamin K depends on age, gender and physiological state, among other factors. Increased requirements are observed in liver disease, malnutrition, and cancer. The FAO (Food and Agriculture Organization of the United Nations) recommendations for adequate intake, expressed in mg of phylloquinone are 55 ug for women and 65 ug for men.[17]

Dietary sources of Vitamin K

Vitamin K1, as stated earlier, is of plant origin. This component is formed in all photosynthesizing plants. Green, leafy vegetables are the main source of its origin and account for approximately 60% of vitamin K1 intake. [18] As shown in Tab.1 parsley, collards or spinach - dark greens containing a lot of chlorophyll, needed for photosynthesis - are also characterized by a high concentration of vitamin K. They contain several times more phylloquinone than the paler iceberg lettuce.

Phylloquinone is also found in olive oil or soybean oil or canola oil, which are so often used in food processing. [21] Dihydrophylloquinone is a transformed form of vitamin K1 during hydrogenation of K1-rich plant oils. This practice was popular especially in the United States, which was used to prolong the life of some oil based products. The fast-food industry in particular uses such practices. However, processed foods are often an overlooked source of vitamin K. Lack of control over the amount of food consumed can rapidly increase a patient's vitamin K level while lowering the INR to dangerous values below therapeutic concentrations. [22] There are differences between the absorption of vitamin K1 and K2. The former is absorbed only 10-15% of the total amount of this vitamin taken in with food, while K2 is absorbed almost completely and has a long biological half-life. When establishing a nutritional plan, the basic element is the absorption of vitamin K in the body. Bioavailability of phylloquinone requires bile and pancreatic juice. It is a fat-soluble vitamin, so adding it to a meal results in higher uptake. [23]

Table.1. Vitamin K sources.

Food type	Form of Vitamin K	Concentration (ug/100g)	References
Vegetables			
Parsley	phylloquinone	1350	[3]
Collards	phylloquinone	440	[19]
Spinach	phylloquinone	380	[19]
Broccoli	phylloquinone	180	[19]
Cabbage	phylloquinone	145	[19]
Iceberg lettuce	phylloquinone	35	[19]
Fats and oils			
Soybean oil	phylloquinone	193	[20]
Canola oil	phylloquinone	127	[20]
Olive oil	phylloquinone	55	[20]
Margarine with hydrogenated oil	dihydrophylloquinone	102	[20]
Hard cheeses	Menaquinone-9	51.1	[19]
Soft cheeses	Menaquinone-9	39.5	[19]
French fries	dihydrophylloquinone	59	[19]
Nachos	dihydrophylloquinone	60	[19]

Patient Adherence to Dietary Recommendations

As many studies show, the patients are expressing difficulties in controlling dietary habits. It is observed that some of the subjects tried to completely restrict foods high in vitamin K. A special group of patients affected by this issue are the ones on plant based diets. [24] Patients receiving anticoagulation therapy are often advised to avoid food containing high vitamin K dosage [25]. It is important to highlight that both vitamin K deficiency and too high vitamin K intake negatively impact the effectiveness of anticoagulant therapy. Suboptimal and especially irregular intake of vitamin K, can cause fluctuation in coagulation factors' production. A useful tool that helps us monitor and optimize treatment is the international Normalized Ratio (INR). [26,30]

The essential part of a patient's adherence to therapy is education. Initially, patients should be informed which products contain high levels of vitamin K. [27] It is important to encourage patients to consume fixed doses of vitamin K, rather than to give up such products entirely, to reduce the risk of both thromboembolic events and bleeding complications. [28] VKA users should be aware of the therapeutic benefits, which can be helpful in compliance e.g. the need for continuous monitoring of INR levels. Another aspect in the use of VKAs is the possibility of drug interactions. A change in treatment or use of multivitamin supplements which often contain vitamin K requires consultation with a clinician. Open communication between patients and healthcare providers is key to managing anticoagulation safely and effectively.

Conclusions

Further research should focus on developing personalized dietary guidelines that incorporate genetic profiling and explore digital tools (e.g., mobile apps or wearable devices) to support dietary tracking and INR monitoring. In addition, further research is needed to clarify optimal intake levels for different forms of vitamin K and assess the long-term outcomes of structured dietary interventions in VKA-treated populations, especially in patients with genetic polymorphisms of the CYP2C9 enzyme. [29]

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