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Hemorrhage After Lunch?

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Abstract

Medication induced hemorrhage during therapy with vitamin K antagonists (VKAs) is a relatively frequent adverse drug reaction. In order to minimize the risk for bleedings patients should take care of their concomitant medication and diet inclusive the dietary supplements. Here we address the question of risk factors of bleeding in patients taking warfarin and other VKAs. Special attention is paid to interactions between food ingredients and the anticoagulant therapy.

Keywords: Vitamin K; Antagonist; Anticoagulant; Warfarin; Food; Herb; Hemorrhage; Interaction; Adverse drug reaction (ADR)

Introduction and Background

To predict risk of adverse reaction to drugs (ARD) is a regular request to medical doctors and pharmacists. It is very hard to give correct answer because of the several circumstances needed to know to give even a very rough estimation. Here we will address the question of risk of bleeding in patients taking a very often used anticoagulant drug warfarin and other vitamin K antagonists (VKAs). In this case food plays a very sensitive role among the other parameters and there are just limited number of publications focusing on food-VKA interaction.

Hemorrhage is a modest or heavy discharge of blood from the blood vessels into the surrounding tissue. It may occure due to several reasons, inclusive high blood pressure, trauma, aneurysm, coagulopathies and its results can be very different, too. There are illnesses that bear the risk of bleeding as well. According to beliefs one of the most serious internal hemorrhage is the cerebral haemorrhage which is one (but less common) form of stroke [1]. Bleedings are known side effects of vitamin K antagonist therapy that is often used to prevent obstructive (ischemic) stroke [2]. Vitamin K deficiency bleeding (VKDB) was first realized as hemorrhagic disease of newborns, but today more cases are to be seen in connection with vitamin K antagonist therapy in the elderly. Superficial haemorrhages (hematomas) in the skin or the sclera are indicators of the improper anticoagulant therapy as well.

Anticoagulants

Anticoagulants are group of drugs that protects people in risk from unintended blood clotting through inhibition of the coagulation cascade. Main reasons of regular taking of anticoagulants is prevent blood cloth (thrombus) formation inside the blood vessels. The main indication of longterm use of anticoagulants is protection against embolism like one type of stroke, deep vein thrombosis and pulmonary embolism, etc. It may be caused by abnormal blood flow, which can be triggered eg. by fibrillation of the heart. The incidence of atrial fibrillation related ischemic stroke rapidly increases with age, doubling for each decade after age 55. In general population prevalence of AF is around 1%, but by 60 it is 2-4% and >80 years of age it is 9-13% per patient-year [3-5].

Main pharmacological groups of anticoagulants are the indirect factor managers (heparin and heparinoids), which accelerate inactivating of antithrombin factor III and the direct thrombin-inhibitors (hirudin and from the recent research eg. dabigatran), the factor Xa inhibitors (eg. rivaroxaban, apixaban), finally the protease synthesis-blockers (vitamin K antagonists). Heparin and heparinoids (mainly low molecule-weight heparin) are used as parenterally administered products. The most prescribed oral anticoagulants are the vitamin K antagonists: the coumarine derivates.

Vitamin K and its Antagonists (VKAs)

Vitamin K (VK) is a group of chemically similar lipophilic molecules however there are two main forms of vitamin K: the K_1 (phylloquinone), which is of plant origin and K_2 (menaquinone), which is of animal and bacterial. Vitamin K has essentially ternary function: participates in the production of proteins indispensible to blood coagulation, it is constitutive part of bone metabolism (synthesis and degradation), have a definitive role in the cell growth (via Gas6 protein) and acts as antioxidant. While VK is fat soluble vitamin it is hardly stored in the body tissues and daily VK intake is needed. Small amount of VK is synthetized by the gut flora. Phylloquinone content of food is taken up from the proximal intestine in presence of bile acids and fatty food. Absorption of vitamin K_2 of bacterial origin takes place in the distal intestine and the colon. Resorption ranges between 20-70%. Average recommended intake of vitamin K is daily 1-1,5 mcg/kg body weight for children and adults as well [6,7].

VK plays an important role in the carboxylation of pro- and anticoagulant proteins, víz. in absence of VK PIVKA (protein induced by vitamin K absence) is produced. The group of these proteins is not able to bind Ca^{++} and phospholipid therefore blood coagulation can not take place. Some structural analogs of VK molecules can antagonize coagulation as well. These analogs, eg. coumarines (phenprocoumon, acenocoumarol and warfarin) are standard of care for over 50 years in anticoagulant therapy because – under certain dosage conditions – they are able to prevent and control thrombus formation. Unfortunately, due to the narrow therapeutic window regular laboratory control and dietary discipline are needed to the safe use of VKAs. Safety of VKA therapy increases with higher time in therapeutic range [8]. Effective therapeutic range can be checked by measurement of international normalized ratio (INR), optimal range of which is between 2 and 3.

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Today, there are more drugs in this indication – the non VKAs, moreover their efficacy is, in certain conditions, better [9]. Actual guideline of the European Society of Cardiology also prefere the new oral anticoagulants for atrial fibrillation [10]. But due to their relatively high cost (to date in many country non-VKA oral anticoagulants are not reimbursed) several ten millions still regularly use VKAs.

Adverse effects of VKAs

The textbook Drug-induced Diseases [11] mentions 0.3-1% serious adverse drug reaction (ADR) incidences of spontaneous haemorrhage in the course of VKA therapy. Serious intracerebral hemorrhage is much less, due to the regular INR-control of the patients on VKA therapy. Light and transient bleedings (subclinical hematomae) are common in patients taking regularly VKAs, ranges between 10-20% of patients per year. In severe bleedings induced by VKAs routine use of prothrombin complex concentrate or infusion of fresh frozen plasma is recommended (the superiority between them is not possible, today [12]). Due to the strong laboratory control, Adam et al. [13] reported better adherence to VKA oral anticoagulants compared to non-VKA oral anticoagulants. Still Bouillon et al. [14] demonstrated in a study following up 17.410 elderly patients for 10 months, that switch from VKA to non-VKA (dabigatran or rivaroxaban) therapy did not increased or decreased the risk of bleeding.

Vitamin K antagonists are teratogenic, therefore during pregnancy its use is of high risk of abortion, stillbirth and malformations of the fetus!

Other ADRs like decreased bone density and increased risk for bone-fractures, increased Ca-oxalate kidney stone formation, higher prevalence of atherosclerosis are mentioned in the literature but the their impact and frequency in different studies are controversial.

The impact of nutrition-drug interactions

The Stockley's Drug Interactions textbook contains under 'warfarin' alone over 600 interacting compounds [15]. Interactions can occur in the pharmacokinetic as well as in the pharmacodynamic phase. In case of pharmacokinetic influencing LADME (liberation, absorption, distribution, metabolism and excretion) steps are affected.

Liberation of active ingredients from dosage forms and the absorption of active compounds are influenced by the drinks and meals that are present in the surrounding of the drugs. The pH, fat- and ioncontent, gastrointestinal motility, hypo- and hyperemia, etc. are here important parameters. Metabolism is influenced mainly by enzyme induction (decrease of effectiveness unless pro-drug is concerned) and enzyme inhibition (decrease in pro-drugs and increase in active drugs). The excretion of drugs and their metabolites depends on perfusion and function of kidneys and the lipofil-hydrofilic substance-character or pH of the urine. All these parameters are influenced by daily food intake.

In 1978 Melander and Wahlin reported a study on 10 healthy subjects who had a standard breakfast after ingestion of 250 mg dicoumarole [16]. They found an average 85% increase in se-coumarin AUC-values after meal in comparison to no breakfast counterparts. Food caused here prolonged drug-retention in the gastrointestinal tract leading to higher rate of liberation and increased absorption of dicoumarol.

In the pharmacodynamic phase pharmacological interaction is realized by influencing receptors from the protein-expression and the receptor sensitivity up to the interference with physiologic mechanisms like voltage-sensitive or ligand-activated membran channels, G-protein coupled transmembrane receptors or enzyme-inhibition.

Ingredients in food can also participate in interactions with drugs and induce adverse effects of drugs used by everybody. The extent of interaction depends on dosage and on genetics. Best-known examples are the VK-containing vegetables and the metabolic changes due to enzyme induction or inhibition.

Let's take an example: Vitamin K deficient bleedings was observed after administration of carbamazepine in an adult on warfarin therapy. Warfarin (especially its S-format and other VKAs, like acenocoumarol and phenprocoumon) is extensively metabolized by the liver enzyme CYP2C9 but CYP3A4 also participate in the metabolism. (Most xenobiotics are subjects of multi-pathway metabolism.) Some compounds like carbamazepine are potent inducer of microsomal enzyme CYP3A4, they affect metabolism of warfarin. In some individuals, due to genetic disposition, the activity of CYP2C9 very poor. VKAs metabolism is not possible or blocked in any extent therefore the pathway through CYP3A4 plays much stronger role in the transformation of VKAs. As the CYP3A4-metabolism of warfarin is accelerated by carbamazepin, clearence (and elimination) of warfarin increases and plasma level (consequently anticoagulant action) decreases. This was the background of the bleeding.

CYP2C9 is a common example of polymorphism and CYP 3A4 is the example of a multifunctional enzyme participating in biotransformation of most of xenobiotics, incl. drugs. Probable similar enzyme-induction is present in case of ginseng or the St John's wort interactions (details see later).

There are also several other options for interaction, as mentioned above. Warfarin is a drug binds strong (99%) to the albumin in the phase of transportation after absorption (It means just 1% of the se-level is active and responsible for the pharmacologic action.). However there are other drugs and xenobiotics competing for binding site of circulating proteins. Should one of them displace warfarin by 5% (binding of warfarin would be actually 95%) means an increase of active circulating warfarin by 500 % and the effect of this change is a huge increase in antagonism of vitamin K and huge impact on hemostasis in toto. By various mechanisms many herbs influence VKA therapy, Leite et al. report 58 plants in this respect [17].

Group of vitamin K-containing foods

There are a lot of lists available on foods containing vitamin K. One can state, however, that there are very limited number of vitamin K-rich food. Some of them contain much more VK in one serving than most people consume over several days. Swiss chard, kale, collards and green asparagus contain 400-850 mcg/100 g VK. Persley contains – depending on growing conditions – the double of that. All these foods can provoke bleedings if patients on VKA therapy consume ca 100 g of these dishes. The fermented Japanese soybean-food, natto, contains ca. 900 mcg K_2 vitamin in 100 g, therefore this is also avoidable for VKA-taking patients.

Important to know that sudden change in eating habits can result in increased bleeding risk for VKA-patients. There might be high intra- and interindividual variability of vitamin K levels in patients [18].

The rapeseed oil, spinach, cabbage, brussel sprouts, endive, spring onions and broccoli contain also relatively high levels of vitamin K (100-200 mcg/100 g). These foods, due to VK content, in dose-dependent manner, also can compensate the effect of vitamin K antagonists and increase risk for bleeding. It is difficult to predict which individuals

are in higher risk because the genetic disposition plays an impotent role, too. There are sporadic reports about food-born bleeding after consumption of foods containing just medium level of vitamin K, eg. liver and seaweed sushi or kidney beans might also have similar effects, under special conditions. Sometimes we meet with surprising cases, too: one report is known about a interaction between warfarin and consumption of mango fruit that incresed INR – after rechallenge – by 10% [19].

Use of dietary supplements

Vitamin K is standard component of multivitamin products in a dose of 5-50 mcg/tablets or dosage form units. As monocomponent products usually K_2 vitamins are put into market, the dose in these products ranges from 20 to 120 mcg. The consumption of such supplements can disturb INR of VKA-patients. Overdosing and consequent intoxication with vitamin K is however almost unknown. Intake of high doses more results in abnormalities of liver function parameters because of liver parenchimal demage and hypercoagulation (shortening of coagulation time). Special sensitivity to vitamin K is known in premature infants therefore the administration in this age should be done carefully due to risk of haemolyse and hyperbilirubinemia. Dietary supplements that contain vitamin K are usually vitamin products and herbal medicines. Sometimes they are fortified by vitamins, included VK, therefore patients on VKA must be cautious.

It should be mentioned that other vitamins can also cause alterations in INR. Hemorrhage was reported by Corrigan and Marcus [20] after taking warfarin and vitamin E together.

Ginseng can in contrast, reduce the anticoagulant effect of VKAs (warfarin and better phenprocoumon) by accelerating metabolism and clearance. It has been suggested that this is due to induction of CYP 3A4 and CYP2C9 enzymes by ginsenosides [21]. St Jone's wort can produce similar effect. By this way enzyme inductors increase risk of thrombus formation in patients taking VKAs.

Conclusion

Vitamin K antagonist reduce the risk of thromboembolic episodes. They are safe and reliable drugs however patients on VKA therapy should stand for stable and effective INR. Although VKAs are very efficacious they carry the risk of bleedings. Patients taking warfarin, phenprocoumon and acenocoumarol should need consultation when they want to stop or start any additional medication, herbal medication or nutritional supplement. In order to minimize bleedings they need to identify risk factors, inclusive the dietary restrictions. Under these conditions there is no need to change VKA therapy to new oral anticoagulants.

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