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Review

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Factors influencing vitamin K antagonists therapy

Factori care influențează terapia cu antagoniști ai vitaminei K

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Abstract

Vitamin K antagonists (VKAs) are widely used for the primary and secondary prevention of thromboembolism, their anticoagulant effect being monitored through INR. Achieving and maintaining a stable anticoagulation status is challenging, because of the narrow therapeutic range, and of the extremely variable individual response to therapy.

Environmental factors such as age, gender, body mass, diet, herbal supplements, drugs, pre-existing pathology, as well as genetic factors can substantially influence the anticoagulant effect of VKAs. The main genetic factors that contribute to individual variability in response to VKAs are genetic polymorphisms in genes influencing VKAs' metabolism (CYP2C9) and pharmacodynamic response (VKOR1) and account for about one third in the variation of warfarin and analogues dose requirement. Systematic genotyping of patients requiring warfarin therapy is still a matter of debate.

Although novel oral anticoagulants (direct thrombin and factor Xa inhibitors) seem promising, VKAs are still frequently prescribed, therefore physicians should be aware of the various factors influencing VKAs' effect, and educational programmes for doctors and patients should be conducted in that respect.

***Keywords**: Vitamin K antagonists, warfarin, drug interactions, genotyping CYP2C9 , VKORC1*

Rezumat

Antagoniștii vitaminei K (AVK) sunt utilizați pe scară largă pentru profilaxia primară și secundară a trombembolismului, efectul lor anticoagulant fiind monitorizat prin intermediul INR. Atingerea și menținerea unui status anticoagulant stabil este adesea dificilă din cauza intervalului therapeutic îngust și a variabilității în răspunsul individual la tratament. Factorii de mediu între care vârsta, sexul, greutatea corporală, alimentația, produsele naturiste și suplimentele alimentare, medicamentele și patologia asociată, precum și factorii genetici pot influența substanțial efectul anticoagulant al AVK. Principalii factori genetici care intervin în răspunsul individual variabil sunt polimorfisme ale genelor responsabile de metabolizarea AVK (CYP2C9) și de răspunsul farmacodinamic (VKORC1), aceștia contribuind cu circa o treime la necesarul variabil al dozei de AVK, analiza genotipică sistematică a pacienților necesitând terapie cu AVK fiind însă un subiect controversat. Cu toate că noile anticoagulante orale oferă o alternativă promițătoare, antagoniștii vitaminei K sunt în continuare prescriși pe scară largă, ceea ce subliniază necesitatea cunoașterii de către clinicieni a factorilor care le influențează efectul, precum și importanța educației pacienților.

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Introduction

Classical oral anticoagulants (OAC) are vitamin K antagonists (VKAs) and are widely used for the primary and secondary prevention of thromboembolic events in patients with atrial fibrillation, prosthetic heart valves and other medical conditions predisposing to thrombosis. In the Western world approximately 15 - 20/1000 subjects use VKAs, and this number is increasing, presumably due to aging of the population (1).

Main vitamin K antagonists include warfarin, acenocoumarol, phenprocoumon, and fluindione. These drugs are not literally vitamin K antagonists, as they don't directly antagonise vitamin K, but act on the recycling of vitamin K, through the inhibition of vitamin K epoxide reductase, which recycles vitamin K to its active form.

The majority of studies in literature are about warfarin, but there are also some studies on acenocoumarol and phenprocoumon (2,3).

Management of OAC treatment is often difficult, because of the narrow therapeutic range, the extremely variable individual response to therapy and several issues in laboratory monitoring. Inadequate anticoagulation management can result either in bleeding or thrombotic events. As achieving and maintaining an optimal anticoagulant status is challenging, both clinicians and laboratory staff should be aware of the multitude of factors interfering with the effect of VKAs and therefore influencing the results of the laboratory monitoring.

The most widely used test in monitoring VKAs' effect is International Normalized Ratio (INR), which tremendously improved the safety and effectiveness of oral anticoagulant treatment with warfarin and related drugs (4). An optimal therapeutic effect is obtained by achieving and maintaining constant INRs within therapeutic range (3).

The anticoagulant response may also be assessed by the "time in therapeutic INR range" (TTR) and "percentage INR in therapeutic range" (% ITTR) (5).

More recently, thrombin generation (TG) assays, such as the calibrated automated thrombography (CAT) assay, were developed as new promising tests in the follow-up of oral anticoagulant therapy, and especially in monitoring the effect of reversal agents in case of overanticoagulation (6,7).

This review aims to briefly discuss the factors that influence the activity of OAC.

The effect of oral anticoagulants is influenced by environmental factors such as patient's compliance, age, gender, body mass, life style, diet, herbal supplements, drugs, pre-existing pathology, as well as by genetic factors. These factors can influence the absorption, pharmacokinetics, and pharmacodynamics of VKAs (8).

Patient's compliance

One of the most important causes of INR instability is patient's noncompliance to VKAs therapy. In a study by Kimmel et al. the proportion of missed tablets was associated with the degree of undercoagulation (9).

Poor comprehension of VKAs indications, due to education level or cognitive impairment were noticed to contribute to treatment non-adherence. Other contributing factors were current living conditions, marital status and employment status (10,11).

Age, gender, body mass, life style

Elderly patients and among them, female subjects tend to have a greater sensitivity to OAC, presumably as a result of reduced availability of vitamin K stores and lower plasma concentrations of vitamin K-dependent clotting factors (8, 12-14).

Subjects with higher total and lean body weight have increased warfarin requirements, possibly through their effect on increasing body surface area. The greater warfarin requirements in females might be attributed to females' smaller body size (15).

Physical activity also seems to play a role in the stability of the response to warfarin. A reduction in the anticoagulant effect has been found to be correlated with a sudden increase in physical activity. The increase in physical activity (consisting in a daily exercise such as walking) resulted in an increase in warfarin dose requirement (16, 17).

Acute alcohol intake may increase anticoagulation by decreasing warfarin metabolism, whereas chronic alcohol ingestion decreases anticoagulation by increasing the clearance of warfarin (18).

Certain components of cigarette smoke may induce CYP1A2, thus increasing warfarin metabolism and resulting in a diminished anticoagulant effect, whereas warfarin dosing requirements have been observed to decrease after smoking cessation (8).

Diet

Vitamin K has an essential role as a cofactor for the carboxylation of glutamic acid, which in its turn is crucial for the activation of coagulation factors II, VII, IX and X as well as for the anticoagulant proteins C, S and Z. Therefore, in patients treated with OAC, a high dietary vitamin K intake may result in the decrease of their anticoagulant response and alternately, a low dietary vitamin K intake leads to a stronger degree of anticoagulation. Prospective studies suggest that this interaction is clinically relevant and might be a major independent factor that interferes with anticoagulation stability.

Phylloquinone or vitamin K_1 is the primary dietary source of vitamin K. Foods containing a great amount of vitamin K are spinach, broccoli, cauliflower, Brussels sprouts, cabbage, lettuce, green peas, cucumber, vegetable oil (soy and canola). Most notable are animal products, including the liver of certain species, cheeses and whole eggs (19).

There is an age-related difference in phylloquinone intakes, the intake being more important in older adults (>55 y), than in younger adults (<45 y) (20). According to Price et al. there were no seasonal differences when phylloquinone intake was assessed during spring, summer, autumn and winter (21).

In patients with unstable INRs, supplementation of VKAs with a daily dose of 100 µg (22) or 150 µg vitamin K (23) was shown to decrease the variability of INR and increase the time in the target range, thus improving the stability of anticoagulant therapy.

In order to optimize the long-term oral anticoagulation, de Assis et al. (24) performed a comparative study on two groups of anticoagulated patients outside their INR target, using an approach based on changes in anticoagulant prescription versus a strategy based on modifications of the amount of vitamin K–rich foods ingested per week. Patients following the dietary vitamin K–guided strategy displayed the same magnitude and direction of INR variation as those with the conventional approach in the short term (15 days), and after 90 days were 16% more likely to be within INR target than

subjects with conventional management. The authors concluded that this strategy is safe and effective, and that the patients should maintain a steady intake of vitamin K after the achievement of anticoagulation stability.

Some studies showed that high-protein diets which increase serum albumin levels may produce an enhanced binding of OAC on serum albumin, thereby diminishing their anticoagulant effect (25, 26).

Herbal products, dietary supplements

In a comprehensive study, Paoletti et al. (27) highlighted the importance of interactions between vitamin K antagonists and herbal products as well as dietary supplements. Prediction of these interactions and characterization of their mechanisms is rather difficult, given the limited information about the pharmacodynamics and pharmacokinetics of these herbal products.

A reduction of OAC efficacy was described in patients taking aloe vera, red ginseng, papaya and green tea supplements. The withdrawal of herbal supplements coupled with augmentation of anticoagulant dosage restored the target INR. An increased anticoagulant effect was observed in patients taking arnica or boswellia-based products, in which the INR was stabilized after the supplements were discontinued.

Large doses of vitamin E may inhibit vitamin K-dependent carboxylase activity and interfere with the coagulation cascade, whereas excess vitamin A appears to interfere with vitamin K absorption, thus enhancing the anticoagulant effect of VKAs (28, 29).

An increased effect of VKAs was described in several cases of patients taking glucosamine and VKAs (30).

These observations emphasize the importance of the physicians being aware of the potential interactions/risks and communicating better with the patients.

Drugs

A large number of drugs are interfering with AVKs. In a study by Wittkowsky et al. it was shown that 81.6% of the 134,833 patients receiving long-term warfarin therapy were prescribed a concurrent prescription for at least one potentially interacting drug, including 64.8% of them who were prescribed one or more concomitant drugs associated with interactions known to increase the INR (31).

As VKAs are metabolized mainly by cytochrome P-450 (CYP) 2C9, the inhibition of CYP 2C9 results in a decreased catabolism of VKAs and a stronger anticoagulant effect, whereas its induction enhances their catabolism and leads to a lower anticoagulant effect. Amiodarone, fluconazole, fluvastatin, fluvoxamine, isoniazid, lovastatin, phenylbutazone are known inhibitors of CYP 2C9, thus potentiating AVKs effect, while barbiturates, namely carbamazepine and rifampicin are inducers of CYP 2C9. Other drugs interact with other cytochromes involved in the metabolism of VKAs, such as quinolones which inhibit CYP 1A2, and macrolides which inhibit CYP 3A4. Fluconazole, miconazole, metronidazole, trimethoprim-sulfamethoxazole are also considered to inhibit CYP 1A2 or CYP 3A4 (14). Antibiotics, which cause decreased production of vitamin K by intestinal microbiota result in an increased sensitivity to VKAs (15). Acetaminophen was shown to enhance the anticoagulant effect of warfarin, thus patients receiving warfarin must monitor their INR more frequently when taking acetaminophen at doses exceeding 2g/day (32).

Associated diseases

A number of pathological conditions may influence VKAs' effects, either by reducing or increasing the dosing requirements.

Liver dysfunction results in an impaired protein synthesis, including vitamin K dependent

factors and in impaired VKAs' metabolism, thus reducing the dosing requirements (33).

The same mechanism might be considered in congestive heart failure, which affects liver function.

An increased sensibility to VKAs is observed in malabsorption syndromes, which affect both vitamin K absorption in the gut and vitamin K synthesis, through alteration of the intestinal microbiota.

Hypercatabolic states such as fever and hyperthyroidism result in an enhanced rate of degradation of vitamin K dependent clotting factors and therefore in reduced dosing requirements (8).

Hypothyroidism decreases the catabolism of the vitamin K clotting factors, therefore, it could be suspected if there is a general trend toward decreased INR values (34).

A high responsiveness to warfarin is noticed in end-stage renal disease, attributable to a diminished activity of CYP2C9 (15).

Genetic factors

The main genetic factors that influence individual variability in response to VKAs are genetic polymorphisms in genes influencing VKAs' metabolism (CYP2C9) and pharmacodynamic response (VKOR1).

Warfarin sensitivity

Warfarin is mainly catabolized through the cytochrome P-450(CYP)2C9, and several studies demonstrated that coding region polymorphisms in CYP2C9 are associated with a slower catabolism of warfarin, resulting in a stronger anticoagulant effect, i.e an enhanced sensitivity to the drug, requiring lower doses.

CYP2C9* 1 represents the wild type allele. Aproximately 40% of the Caucasian population express one or both of the two variant alleles, CYP2C9*2 and CYP2C9*3 which display only 70% and 5% of catabolic efficiency, respectively, compared to the wild type allele. CYP2C9*2 and CYP2C9*3 alleles are considered to be risk factors for over-anticoagulation if patients are given standard doses of warfarin (35).

In other ethnic groups the pattern and prevalence of CYP2C9 alleles are different from that in Caucasians. In patients of African descent, two other alleles are selectively expressed, CYP2C9*5 and CYP2C9*6, both being functionally defective (36), while in Asian subjects defective alleles that have been detected are CYP2C9*4, CYP2C9*13, CYP2C9*25,*26,*28 and *30 (37).

Muszkat et al. studied the influence of CYP2C9 polymorphisms in the presence of drug-disease and drug-drug interactions and concluded that CYP2C9 *1/*3 genotype, older age, and the use of antibiotics were associated with 33% lower warfarin dosage requirements and INR values higher than the therapeutic range of 3 (38).

Warfarin resistance

Warfarin resistance is caused by mutations in the genes encoding vitamin K epoxide reductase complex 1 VKORC1. This complex is responsible for the recycling of reduced vitamin K, which is necessary for the post-translational gamma carboxylation of vitamin K dependent factors (39).

Several rare miss-sense mutations in VKORC1 were described in warfarin resistant patients, but not in the general population (40). This observation suggests that coding – region polymorphisms probably do not explain the variability of warfarin dose in individual patients.

In contrast, a single nucleotide polymorphism (1639 G > A) in the non-coding region of VKORC1 was found to be associated with an increased sensitivity to warfarin across normal dosing range. The 1639G >A allele frequency is

the major allele (about 90%) in Asian population and it is also quite frequent in Caucasians (40%) (41).

In patients requiring high doses of warfarin to reach the target INR one should not forget that genetic warfarin resistance is rare (< 0.1%) , thus another factors such as poor adherence to therapy, laboratory errors and interactions should be taken into account (42).

Polymorphisms of the VKORC1 and CYP2C9 genes account for about one third in variation of warfarin and analogues dose requirements, and together with other factors such as age, gender, body mass index, interacting drugs and dietary intake of vitamin K attain to approximately 55% of inter-individual variability dose requirements. Pharmacodynamics of warfarin is influenced by a multitude of other genetic factors, including polymorphisms in apolipoprotein E, multi drug resistance 1 (MDR1), genes encoding vitamin K-dependent clotting factors and possibly genes encoding additional components of the vitamin K epoxide reductase complex (43, 44).

The strategy of systematic genotyping before or during the treatment with VKAs is still a matter of debate (45). In a randomized trial Pirmohamed et al. concluded that genotype guided warfarin dosing was superior to standard dosing (46).

On the other hand in a meta-analysis of randomized clinical trials, a genotype-guided dosing strategy did not result in a greater percentage of time that the INR was within the therapeutic range, fewer patients with an INR greater than 4, or a reduction in major bleeding or thromboembolic events compared with clinical dosing algorithms (47).

Conclusion

As presented above, classical OAC have many shortcomings, pertaining to both environmental and genetic factors.

The emerging novel anticoagulants such as oral direct thrombin inhibitor (Dabigatran) and direct factor Xa inhibitors (Rivaroxaban, Apixaban and Edoxaban) seem promising, given their few drug and dietary interactions, their broad therapeutic interval and the administration of fixed drug doses with no need for monitoring. However, there are some issues with this new therapeutic class, such as the absence of specific antidotes, uncertainty about dosing in patients with extreme body weight or renal dysfunction, unavailability of assays for measuring drug levels in most laboratories and, last but not least, higher costs compared to VKAs (48).

As vitamin K antagonists are still widely prescribed, physicians should be aware of the various factors influencing VKAs' effect, and educational programmes for doctors and patients should be conducted in that respect.

Abbreviations

CYP2C9	cytochrome P-450 2C9
INR	International Normalized Ratio
MDR	multidrug resistance
OAC	oral anticoagulants
TTR	time in therapeutic range
VKAs	vitamin K antagonists
VKORC1	vitamin K epoxide reductase complex 1

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