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Disadvantages of VKA and requirements for novel anticoagulants

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Vitamin K antagonists have been in wide use for over 70 years. Warfarin, the most commonly used vitamin K antagonist, has been shown to be highly effective in treating and preventing thrombosis. Despite this, warfarin has many disadvantages, which has led to the development of a new class of oral anticoagulants targeted to specific coagulation factors designated as target-specific oral anticoagulants (TSOAs). TSOAs include the thrombin inhibitors (dabigatran) and factor Xa inhibitors (rivaroxaban, apixaban). This chapter reviews the disadvantages of warfarin and evaluates both the advantages and disadvantages of the new oral anticoagulants.

Introduction

The vitamin K antagonists have been in wide use since the 1940's with warfarin being the most commonly used vitamin K antagonist. Warfarin is highly effective in treating and preventing thrombosis, but despite its prolific use, warfarin has many disadvantages. These include a narrow therapeutic index, delayed onset and offset of effect, limitations secondary to genetics, multiple drug interactions, interactions with dietary vitamin K intake, and requirements for monitoring and high quality dose management. With these various limitations there has been a recent focus on the need for new oral anticoagulants, and a new class of target-specific oral anticoagulants has been developed. The advantages of these new oral anticoagulants compared to warfarin include a rapid onset of therapeutic effect, fewer drug interactions, fixed dose response relationships without the requirement for monitoring, and cost-effectiveness. However, there also are notable disadvantages of these novel drugs,

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which include reliance on renal elimination, the absence of a reversal agent, gastrointestinal bleeding, and compliance issues.

Disadvantages of vitamin K antagonists

Warfarin has no intrinsic activity but acts as an indirect anticoagulant with multiple targets [1]. Warfarin acts by inhibiting *microsomal vitamin K epoxide reductase*, which normally converts vitamin K 2,3-epoxide, an inactive metabolite of vitamin K, to reduced active vitamin K. Vitamin K is necessary for the post-translational carboxylation of glutamate residues for synthesis of coagulation factors II, VII, IX, and X. Thus, by inhibiting the inter-conversion of vitamin K to its active form warfarin achieves an anticoagulant effect [2,3].

Slow onset and slow offset

Warfarin is rapidly absorbed from the gastrointestinal tract with high oral bioavailability and maximum concentrations in the blood are reached 90 min after administration [4]. It is a racemic mixture of two steroisomers, S and R isomers. The S isomer is the more potent form and has a separate route of metabolism. With warfarin, it takes several days to lower levels of vitamin K dependent coagulation factors. The delayed onset of its antithrombotic effect can be attributed to the long half-life of factor II, prothrombin, which is 60–72 h [4]. Because of a delayed onset, warfarin often requires initial bridging therapy with a rapidly acting parenteral anticoagulant such as unfractionated heparin or low-molecular-weight heparin. This requires the inconvenience of hospitalization or complex arrangements for outpatient administration [5]. Initial bridging therapy with heparins is necessary to avoid a potential hypercoagulable state early in therapy induced by warfarin's effect on protein C, which has a short half-life of approximately 6 h. Without bridging therapy there is a heightened risk for recurrent thromboembolism in the first three months after the initial episode of venous thromboembolism, especially in the first few weeks [5]. This phenomenon may also be responsible for an increased risk of stroke during initial warfarin therapy in patients with atrial fibrillation [6,7]. Warfarin also has a slow-offset of action with a half-life of 36–42 h. This may be problematic for patients requiring immediate surgical interventions. It is recommended that for patients with a high risk for thromboembolism, warfarin should be stopped approximately four or five days before surgery to allow the INR to return to normal and replaced with a short acting heparin that can be stopped shortly before surgery and restarted after the procedure [4].

Genetics

Pharmacogenetics plays an important role in warfarin metabolism and vitamin K inhibition and accounts for much of the inter-patient variability in dose response. The more active form of warfarin, the S-isomer, is metabolized by the cytochrome P450 enzyme, CYP2C9, which accounts for 80–85% of its overall elimination [8]. Nucleotide polymorphisms alter the function of CYP2C9 such that carriers of two distinct predominant alleles impair the metabolism of warfarin and require lower doses to achieve and maintain therapeutic levels. The vitamin K epoxide reductase complex 1 (VKROC1), the target of warfarin's activity, is also impacted by polymorphisms that lead to an enzyme that is either more or less sensitive to warfarin's effect. Polymorphisms in the genes controlling these two proteins have been shown to account for as much as 50–60% of the variability in warfarin dose requirements [9].

The influence of pharmacogenetics on warfarin dosing is yet another example of the disadvantages of the medication. Because of the impracticality of rapid turnaround genetic tests and concerns regarding cost-effectiveness, routine pharmacogenetic profiling is not currently recommended [10]. Patients with certain genetic profiles are at risk for supra-therapeutic and sub-therapeutic INR levels. The risk is increased when other factors come into play such as diet and concomitant drug interactions.

Drug and food interactions

More than 120 drug and food interactions with warfarin have been described over the years [11]. With a narrow therapeutic index, minor changes in metabolism can lead to major clinical problems