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Warfarin Therapy: New Challenges of an Old Drug

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Abstract

The anticoagulant drug warfarin is a vitamin K antagonist (VKA), coumarin derivative, formed by the racemic mixture of two optically active isomers known by Rectus (R) and Sinister (S) enantiomers in equal proportion, being the S-warfarin five times more potent. Although warfarin is still considered the mainstay of oral anticoagulant treatment, it is a difficult drug to manage due to its narrow therapeutic index. An inappropriate management of patients can lead to subtherapeutic or supratherapeutic levels, increasing the risk of thromboembolic episodes or hemorrhagic episodes, respectively. Common indications for the use of warfarin include stroke prevention in atrial fibrillation, preventing thrombus formation in patients with heart valves and treatment of venous thromboembolism. Unlike situations as nonvalvular atrial fibrillation (and thromboembolic risk factors such as hypertension, diabetes or ventricular dysfunction), venous thrombosis and pulmonary embolism where there is evidence for the use of the new oral anticoagulants (dabigatran, apixaban, rivaroxaban, etc), warfarin and similar remain only option for patients with cardiac valve prosthesis requiring anticoagulation.

Keywords: Warfarin; Anticoagulants; Antithrombotics

Introduction

In 1939, a hemorrhagic agent called bis-hydroxycoumarin (dicoumarol) was identified from a hemorrhagic disorder detected through of ingestion the spoiled sweet clover silage by cattle [1]. Then in 1948, a compound named warfarin (name derived from Wisconsin Alumni Research Foundation) with a more potent action has been discovered and then studies conducted by biopharmaceutical assays began to be considered one of most widely used anticoagulant therapy drugs worldwide [2].

Pharmacokinetics and Pharmacodynamics

The anticoagulant drug warfarin is a vitamin K antagonist (VKA), coumarin derivative, formed by the racemic mixture of two optically active isomers known by Rectus (R) and Sinister (S) enantiomers in equal proportion, being the S-warfarin five times more potent. It is normally administered as the racemate and its effect is observed normally within two to seven days after initiation of therapy, according to the administered dose [3,4].

Warfarin acts by interfering in the interconversion of cyclic 2,3 vitamin K epoxide. The vitamin K epoxide reductase is inhibited by therapeutic doses of warfarin inhibiting thus the synthesis of vitamin K-dependent factors, leading to inhibition of γ-carboxylation of clotting factors II, VII, IV and X, and the anticoagulant proteins C and S. Effects on prothrombin time are produced in 24 to 36 hours after the initial dose and reach the maximum plasmatic concentration in 36 to 48 hours, maintained for 48 hours or more after discontinuance of dosing [2].

It is rapidly absorbed by the gastrointestinal tract and shows high biodisponibility, and reaches maximal blood concentrations about 90 min after oral administration. The absorption suffers no food influence. It has a low volume of distribution (0.14 L/kg) and a high binding rate to plasma proteins, specifically albumin (99.0%); displays hepatic metabolism via the complex multienzymatic cytochrome P450 (CYP) by CYP2C9 isoenzymes (primary isoenzyme), CYP2C19, CYP2C8, CYP2C18 and CYP3A4. Its metabolites are inactive and present in renal excretion (92.0%) and to a lesser extent in bile. It has a half-life of a week (168 h) [5].

Some point mutations may bring on alterations in its pharmacokinetics and pharmacodynamics. There have been already reported mutations at the molecular level that alter the functions of encoding gene for both CYP2C9 and vitamin K epoxide reductase complex 1 (VKORC1) and among these mutations the SNP in CYP2C9*2 and CYP2C9*3 positions are highlighted [6].

The enzyme encoded by CYP2C9 is the most importantly involved in the pharmacokinetics of coumarin, especially warfarin. While the main gene involved in the pharmacodynamics is the VKORC1 encoding the target enzyme of coumarin. Both genes have been widely studied taking into consideration the pharmacogenomics approach and its role with the aim to improve the warfarin therapeutic response [6-8]. Genetic mutations in the gene coding for the VKORC1often

involve several mutations leading to various haplotypes that cause greater resistance to warfarin therapy.

VKAs are highly susceptible to drug-drug interactions. For warfarin, for example, manufacturer-provided product information lists >200 specific agents that may interfere with this agent. The most effective method to avoid adverse outcomes associated with drug interactions is to try to avoid, when feasible, concurrent use of potentially interacting drugs and to use noninteracting alternatives instead. When noninteracting alternatives are not available, adverse outcomes can be avoided by increasing the frequency of monitoring and adjusting warfarin doses based on INR response. Prospective dosing adjustments are inappropriate because of the unpredictable nature of patient response to drug interactions [9].

Clinical Management

Although warfarin is still considered the mainstay of oral anticoagulant treatment, it is a difficult drug to manage due to its narrow therapeutic index. An inappropriate management of patients can lead to subtherapeutic or supratherapeutic levels, increasing the risk of thromboembolic episodes or hemorrhagic episodes, respectively. Common indications for the use of warfarin include stroke prevention in atrial fibrillation, preventing thrombus formation in patients with heart valves and treatment of venous thromboembolism [10].

To standardize the report of anticoagulation levels around the world, in 1982 the World Health Organization's Expert Committee on Biologic Standardization developed the International Normalized Ratio (INR), which became the main laboratory measurement used to determine the effects of oral anticoagulants.

The view that warfarin exerts its antithrombotic effect by reducing prothrombin levels is consistent with observations that clot-bound thrombin is an important mediator of clot growth and that reduction in prothrombin levels decreases the amount of thrombin generated and bound to fibrin, thereby reducing thrombogenicity. The responsiveness of a thromboplastin can be measured by assessing its international sensitivity index (ISI). The ISI reflects the responsiveness of a given thromboplastin to the reduction of the vitamin K-dependent coagulation factors compared with the primary World Health Organization (WHO) international reference preparations, so that the more responsive the reagent, the lower the ISI value. The INR is based on ISI values derived from the plasma of patients who had received stable anticoagulant doses for at least 6 weeks. As a result, the INR has not been validated and should be viewed with some skepticism early in the course of warfarin therapy, particularly when results are obtained from different laboratories [9].

For most warfarin indications, the therapeutic INR range is 2.0 to 3.0. However when it is used for mechanical mitral valve or combined mitral and aortic valves, the range is 2.5 to 3.0. Maintenance of this narrow INR target is important to avoid risk of bleeding complications with a higher INR and thromboembolic events with a lower one [11].

Warfarin has a wide variation regarding onset/offset of action and it is heavily influenced by drug-drug and food-drug interactions, genetic variations, alcohol consumption and comorbidities. Therefore some fluctuations in INR levels can be expected, which requires close follow up of patients, particularly in the first three months of treatment [11,12]. A systematic review published in 2012 consistently showed that among long-term care residents using warfarin, INRs were in the target range only for approximately half of the time. Also on that study there was evidence that only 20% of the residents exceeded 60% of monitored time in therapeutic range, most of them spending a long time at subtherapeutic INR levels [13]. Furthermore, in a subgroup of antiphospholipid syndrome patients, INR monitoring may not be safe for determining the dose of warfarin because their INR values can be falsely elevated [14].

Initiation of Warfarin therapy is challenging since the pharmacodynamic response is delayed and hard to predict. Alterations in warfarin dosage can take several days to affect INR level. Besides, drug-drug or drug-food interactions play a great role on influencing the effect of anticoagulation [13]. Most of the clinically relevant interactions involve a few mechanisms and are attributed to many classes of drugs. In concomitant use with warfarin, drugs that interfere in platelet function such as acetylsalicylic acid and clopidogrel increase the risk of hemorrhage without raising the INR. Non-steroidal antiinflamatory drugs may increase the risk of bleeding due to injury to the gastrointestinal mucosa. Some antibiotics alter the balance of gut microflora, enhancing the effect of warfarin and therefore increasing the risk of hemorrhage [15]. Other drugs affect the absorption, protein binding, vitamin K catabolism or hepatic metabolism of warfarin [9].

Among those, the most significant interactions involve the induction or inhibition of warfarin hepatic metabolism, through the cytochrome P450 pathway, which is the primary site of S-warfarin metabolism. Drugs commonly involved on that include amiodarone, statins, anticonvulsants and antibiotics such as quinolones and macrolides as well as azoles [9]. Other several drugs including some antidepressants, levothyroxine, acetaminophen, clofibrate, cephalosporines and herbal therapies such as "ginseng", "garlic" and "ginko biloba" also have been shown to interact with warfarin [16,17].

Variations in vitamin K consumption also can affect the anticoagulant response to warfarin, increasing or decreasing its effect. Foods that contain the highest amount of vitamin K per serving are green leafy vegetables. Many patients believe these foods should be avoided from their diet once they take warfarin, however they should be advised that the key is to constantly consume a balanced amount of vitamin K rich foods [16]. Regarding alcohol ingestion, whilst regular and moderate alcohol consumption has little effect on anticoagulation control, an increased consumption may importantly affect it.

Due to its narrow therapeutic index and complex net of interactions with other drugs and foods, patients using warfarin should be advised not to take over-the-counter medicines, herbal products or food supplements without before consulting their doctor. More frequent monitoring of the INR should be proposed if dietary habits have substantially changed in response to weight reduction diets, periods following hospitalization, treatment with chemotherapy, sustained diarrhea or vomiting, or in case of anorexia [9].

Previous studies have raised interest in using the genotyping of CYP2C9 and VKORC1 to guide warfarin dosing. However, there is lack of solid evidence to prove that genotype plus clinical algorithm provides improved clinical outcomes than the single clinical algorithm [18-20]. Allocation to genotype plus clinical algorithm may be associated with a significant improvement of the percentage of time within the therapeutic INR range for patients adopting fixed dose of warfarin. But, in a recent meta-analysis [21], the incidence of total adverse events and death rates did not differ between these two groups.

Regarding the use of antithrombotic therapy for deep vein thrombosis (DVT) or pulmonary embolism (PE), the anticoagulants remain the treatment of choice since the introduction of parenteral heparin in the 1930s. The parenteral anticoagulant is then overlapped with a VKA (e.g. warfarin) until the latter has reached its target anticoagulation level, after which the parenteral agent is discontinued. VKA are almost always a great option is this scenario, recommending a therapeutic INR range of 2.0 to 3.0 (target INR of 2.5) [22]. Non-VKA direct oral anticoagulants, fast-acting, single-target, provide a simplified option for VTE treatment because presents more predictable pharmacological properties than VKAs and fewer drug interactions, besides not need routine coagulation monitoring. Phase III studies have investigated rivaroxaban and apixaban as single-drug approaches, and edoxaban and dabigatran in conjunction with initial heparin therapy. These agents demonstrated non-inferiority to standard therapy, and most showed significant reductions in major bleeding [23].

Unlike situations as nonvalvular atrial fibrillation (and thromboembolic risk factors such as hypertension, diabetes or ventricular dysfunction), venous thrombosis and pulmonary embolism where there is evidence for the use of the new oral anticoagulants (dabigatran, apixaban, rivaroxaban, etc), warfarin and similar remain only option for patients with cardiac valve prosthesis requiring anticoagulation. The only randomized clinical trial comparing warfarin with a new oral anticoagulant was terminated early because showed increased rates of thromboembolic and bleeding events in dabigatran treatment arm [24], leading the U.S. Food and Drug Administration (FDA) to contraindicate its use in these patients [25]. Currently, there is an ongoing pilot study in Brazil comparing dabigatran with warfarin in patients with cardiac valve bioprosthesis who developed atrial fibrillation after operative [26]. The results of this study maybe will open new opportunities for research in this area.

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