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REVIEW

Old and new oral anticoagulants: Food, herbal medicines and drug interactions

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ABSTRACT

The most commonly prescribed oral anticoagulants worldwide are the vitamin K antagonists (VKAs) such as warfarin. Factors affecting the pharmacokinetics of VKAs are important because deviations from their narrow therapeutic window can result in bleedings due to over-anticoagulation or thrombosis because of under-anticoagulation. In addition to pharmacodynamic interactions (e.g., augmented bleeding risk for concomitant use of NSAIDs), interactions with drugs, foods, herbs, and over-the-counter medications may affect the risk/benefit ratio of VKAs. Direct oral anticoagulants (DOACs) including Factor Xa inhibitors (rivaroxaban, apixaban and edoxaban) and thrombin inhibitor (dabigatran) are poised to replace warfarin. Phase-3 studies and real-world evaluations have established that the safety profile of DOACs is superior to those of VKAs. However, some pharmacokinetic and pharmacodynamic interactions are expected. Herein we present a critical review of VKAs and DOACs with focus on their potential for interactions with drugs, foods, herbs and over-the-counter medications.

1. Introduction

Until recently, the vitamin K antagonists (VKAs) were the only oral anticoagulant agents available, and warfarin remains the most commonly prescribed oral anticoagulant worldwide. Its indications include a wide range of clinical conditions from prevention of cardioembolic ischemic stroke to deep venous thrombosis and pulmonary embolism. Anticoagulants are used in patients with a history of atrial fibrillation or flutter, recent major surgery or immobility, heart valve replacement, ischemic stroke or other thrombotic event [1]. Warfarin has significant variability in dose-response across individuals and a narrow therapeutic window (the international normalized ratio [PT-INR] value must remain between 2.0 and 3.0 for most indications) [2]. Clinical outcomes are highly correlated with the amount of time patient's PT-INR values are maintained in range [3]. Patients with an average individual time in therapeutic range >70% are considered to be at a low risk of a major hemorrhagic or thrombotic event [4]. Frequent monitoring of PT-INR lab values and dose adjustments, therefore, are necessary for safe and efficacious use of warfarin [5]. Likewise, patient instruction and identification of factors leading to over- or under-anticoagulation are critical [6,7]. When combined with low-dose aspirin, non-steroidal anti-inflammatory drugs (NSAIDs) or clopidogrel, warfarin acts cumulatively, and risk of bleeding is significantly increased [8,9]. VKAs are among the medications with the highest incidence of drug-related life-threatening events [1] and top the list of interactions with foods, herbal supplements, prescribed drugs and over-the-counter medications [10,11]. Interactions resulting in over- or under-anticoagulation drastically increase the risk of major hemorrhagic or thrombotic event.

Direct oral anticoagulants (DOACs), approved for the prevention and treatment of venous thromboembolism and of systemic and cerebral embolism in atrial fibrillation [12], are poised to replace warfarin for stroke prevention [13]. As their anticoagulant effect is more predictable and stable (i.e., less influenced by interactions with foods, herbal supplements, prescribed drugs and over-the-counter medications), DOACs should prove safer and less problematic compared to the VKAs [14]. Clinical studies of venous and arterial thromboprophylaxis suggest that routine laboratory monitoring is not necessary with thrombin inhibitors or Factor Xa inhibitors. However, potential pharmacodynamic interactions and drug interactions with foods, herbal supplements, prescribed drugs and over-the-counter medications must still be considered with the use of DOACs [15].

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2. Vitamin K antagonists (VKAs)

The pharmacokinetic and pharmacodynamic effects on VKAs that result from interactions with foods, herbal supplements, prescribed drugs and over-the-counter medications are summarized in Table 1, and detailed in the Online Appendix. A variety of drugs, herbal medicines, nutrients that may affect dietary intake of Vitamin K may interact with VKAs possibly changing their effect [16]. Mechanisms of such interactions are herein discussed.

2.1. Drug-drug interactions affecting pharmacokinetic of warfarin

Several prescriptions and over-the-counter medications, foods and herbal supplements alter the pharmacokinetics (absorption, distribution, metabolism and elimination) and pharmacodynamics (anticoagulant effect) of warfarin (Table 1) [17,18].

The absorption of warfarin is reduced by concomitant use of cholestyramine and sucralfate [19]. As warfarin is highly bound to plasma proteins, other substances or medications that compete for protein-binding sites (e.g., ibuprofen, quinidine, fenofibrate, losartan, valsartan, amlodipine, felodipine, sulfinpyrazone, phenylbutazone and the principal metabolite of chloral hydrate. i.e. trichloracetic acid) displace warfarin, potentiating the anticoagulant action of VKAs [20]. This effect, often observed as marginally increased PT-INR, is typically transient and has a delayed onset ranging from 1 day to 3 weeks (in the case of phenprocoumon) after starting the concomitant drug regimen [21,22].

The majority of drug interactions affecting warfarin involves inhibition of the expression and/or activity of CYP450 enzymes involved in warfarin metabolism (CYP2C9 for the *S*-enantiomer and CYPs 1A2, 2C19, 3A4 for *R*-enantiomer of warfarin). Interactions involving the *S*-enantiomer may be of greater impact because the activity (anticoagulant effect) of the *S*-enantiomer is 2 to 5-fold greater than that of the *R*-enantiomer [23]. The concomitant use of medications that induce CYP2C9 (e.g., rifampin and phenobarbital) results in increased clearance of warfarin and thus less anticoagulation [24].

Nearly 1 in 3 patients prescribed warfarin also prescribed a statin. Several statins are metabolized by CYP3A4 and CYP2C9 isoenzymes. Altered warfarin metabolism leading to increase PT-INR values has been reported with concomitant use of fluvastatin, lovastatin, simvastatin or atorvastatin [25,26]. As the metabolism of pravastatin and rosuvastatin does not involve CYP450 enzymes, potential for drug-drug interactions with warfarin is limited [27,28]. Other cardiovascular pharmacotherapies that interact with warfarin are listed in Table 2.

HIV-positive patients often require anticoagulation therapy because they are at increased risk of venous thromboembolism or cardiovascular disease [29]. As several of the anti-retroviral agents (e.g., nevirapine, efavirez, saquinavir and ritonavir) used to treat HIV interact with warfarin metabolism by inhibiting/inducing CYP enzymes (Table 3), clinicians treating HIV-positive patients should be informed about the increased likelihood of adverse reactions or decreased efficacy of warfarin therapy in this patient population [30,31,32,33].

Some of the anti-fungal drugs (e.g., fluconazole, miconazole), and antibiotics (e.g., azithromycin, ciprofloxacin) inhibit specific CYP450 iso-enzymes (Table 3), altering warfarin pharmacokinetics and increase PT-INR values and risk of hemorrhage when combined with warfarin [22,34]. In addition, they can also diminish gut absorption of Vitamin K by altering the gut flora. Although this is rarely of clinical significance (other than in malnourished patient populations), this altered ability to absorb vitamin K can result in lowered synthesis of vitamin K-dependent coagulation proteins and, ultimately, in an increased risk of hemorrhage [35].

Several over-the-counter medications significantly alter warfarin metabolism. Increased PT-INR and pro-hemorrhagic effects (e.g. ecchymosis, subcutaneous hematomas, hematuria) have been reported after 2 weeks of concomitant use of over-the-counter anti-fungal "Miconazole (oral gel)", a strong CYP2C9 inhibitor, used for the treatment of oral Candidiasis [36]. Two case reports of decreased PT-INR values with concomitant use of over-the-counter menthol drops (antitussives) provide another example of potential interactions between warfarin and over-the-counter medications [37,38].

Drug-drug interactions may also affect warfarin elimination. For example, the concomitant use of miconazole and phenylbutazone results in increased warfarin elimination and decrease efficacy of warfarin therapy, by inhibiting the elimination of the *S*-enantiomer [16].

Table 1
Effect of commonly employed drugs on PT-INR [18,28].

Drugs that increase PT-INR	Drugs that lower PT-INR
Drugs active on the central nervous system	
Citalopram[a]	Barbiturates[a]
Disulfiram	Carbamazepine[a]
Entacapone[a]	Chlordiazepoxide
Phenytoin	Propofol
Fluoxetine	Ethanol
Propoxyphene	
Fluvoxamine	
Anti-inflammatory drugs	
Acetaminophen	Azathioprine
Allopurinol	Mesalazine
Celecoxib	Sulfasalazine
Dextropropoxyphene	
Indomethacin	
Interferon	
Methyl-prednisolone	
Phenylbutazone	
Piroxicam[a]	
Sulindac	
Sulfinpyrazone	
Tramadol	
Other	
Cimetidine[a]	Chelating agents
Omeprazole	Cyclosporine
Orlistat	Etretinate
CMF	Anti-flu vaccine
Danazol	Menthol (anti-cough)
5-fluorouracil	Mercaptopurine
Ifosphamide	Methimazole
Levamisole	Multivitamin supplies
Levonorgestrel	Raloxifene
Tamoxifen	
Zileuton[a]	

[a] Clinically relevant interactions with warfarin.

Table 2
Cardiovascular drugs interfering with the metabolism/clearance of warfarin [28].

Drug [Reference(s)]	Mechanism(s)
Drugs that increase PT-INR	
Acetyl-salicylic acid	Pharmacodynamics
Amiodarone[a] [24]	Moderate inhibitor of CYP3A4, CYP1A2, CYP2C9
Dronedarone[a] [168,171]	Moderate inhibitor of CYP3A4, inhibitor of P-gp
Atorvastatin [172]	Inhibitor of CYP3A4
Quinidine [173]	Inhibitor of CYP3A4
Clofibrate[a] [174]	Inhibitor of CYP3A4
Diltiazem[a] [28]	Inhibitor of CYP3A4
Disopyramide [175]	Inhibitor of CYP3A4
Fenofibrate[a] [172]	Inhibitor of CYP3A4
Glucagon [176]	Inhibitor of CYP3A4
Lovastatin [172]	Inhibitor of CYP3A4
Propafenone[a] [177]	Inhibitor of CYP3A4
Propranolol[a] [178]	Inhibitor of CYP1A2
Rosuvastatin [179]	Inhibitor of CYP3A4
Simvastatin [25]	Inhibitor of CYP3A4
Drugs that lower PT-INR	
Cholestyramine [28]	Interference with warfarin absorption
Telmisartan [180]	Inhibitor of CYP3A4

[a] Clinically relevant interactions with warfarin.