

Mechanism of action of warfarin biology essay



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Warfarin is an anticoagulant medication that is used to prevent thrombosis (clots) and embolism in many disorders. Warfarin activity has to be monitored by frequent blood testing for the International Normalized Ratio (INR). Warfarin is a synthetic derivative of coumarin, a chemical found naturally in many plants — it decreases blood coagulation by interfering with vitamin K metabolism.

Mechanism of Action of Warfarin

Warfarin is vitamin K antagonist that produce it's anticoagulant effect by interfering with the cyclic interconversion of vitamin K and its 2, 3 epoxide (vitamin K epoxide). Vitamin K is a cofactor for the posttranslational carboxylation of glutamate residues to γ -carboxyglutamates on the N-terminal regions of vitamin K-dependent proteins (Whitlon, et al., 1978; Fasco, et al., 1982)

. 123456 These coagulation factors (factors II, VII, IX, and X) require γ -carboxylation for their biological activity. Coumarins produce their anticoagulant effect by inhibiting the vitamin K conversion cycle, thereby causing hepatic production of partially carboxylated and decarboxylated proteins with reduced procoagulant activity. 78 In addition to their anticoagulant effect, the vitamin K antagonists inhibit carboxylation of the regulatory anticoagulant proteins C and S and therefore have the potential to exert a procoagulant effect.

In the presence of calcium ions, carboxylation causes a conformational change in coagulation proteins⁹¹⁰¹¹ that promotes binding to cofactors on phospholipid surfaces. The carboxylation reaction requires the reduced form

of vitamin K (vitamin KH₂), molecular oxygen, and carbon dioxide, and is linked to the oxidation of vitamin KH₂ to vitamin K epoxide. Vitamin K epoxide is then recycled to vitamin KH₂ through two reductase steps. The first, which is sensitive to vitamin K antagonists, reduces vitamin K epoxide to vitamin K₁ (the natural food form of vitamin K₁), while the second, which is relatively insensitive to vitamin K antagonists, reduces vitamin K₁ to vitamin KH₂. Treatment with vitamin K antagonists leads to the depletion of vitamin KH₂, thereby limiting the γ -carboxylation of the vitamin K-dependent coagulant proteins. The effect of coumarins can be counteracted by vitamin K₁ (either ingested in food or administered therapeutically) because the second reductase step is relatively insensitive to vitamin K antagonists (Fig 1). Patients treated with a large dose of vitamin K₁ can also become warfarin resistant for up to a week because vitamin K₁ accumulates in the liver and is available to the coumarin-insensitive reductase.

Pharmacokinetics and Pharmacodynamics of Warfarin

Warfarin is a racemic mixture of two optically active isomers, the R and S forms in roughly equal proportion. It has high bioavailability, 1920 is rapidly absorbed from the GI tract, and reaches maximal blood concentrations in healthy volunteers in 90 min after oral administration. 1921 Racemic warfarin has a half-life of 36 to 42 h, circulates bound to plasma proteins (mainly albumin), and accumulates in the liver where the two isomers are metabolically transformed by different pathways. 22 The dose-response relationship of warfarin is influenced by genetic and environmental factors, including a recently identified common mutation in the gene coding for one

of the common cytochrome P450 enzymes (2C9), the hepatic enzyme responsible for oxidative metabolism of the warfarin S-isomer. 2324 This mutation likely contributes to the variability in dose response to warfarin among healthy subjects. 25 In addition to known and unknown genetic factors, various disease states, drugs, and dietary factors can interfere with the response to warfarin.

The anticoagulant response to warfarin is influenced by pharmacokinetic factors, including drug interactions that affect the absorption or metabolic clearance of warfarin, and pharmacodynamic factors that alter the hemostatic response to given concentrations of the drug. Variability in anticoagulant response also occurs as a result of inaccuracies in laboratory testing, patient noncompliance, and miscommunication between patient and physician. Other drugs may influence the pharmacokinetics of warfarin by reducing GI absorption or by disrupting its metabolic clearance. For example, the anticoagulant effect of warfarin is reduced by cholestyramine, which impairs its absorption, and is potentiated by drugs that inhibit warfarin clearance through stereoselective or nonselective pathways. 252627

Stereoselective interactions affect oxidative metabolism of either the S-isomer or R-isomer of warfarin. 2627 Inhibition of S-warfarin metabolism is more important clinically because this isomer is five times more potent as a vitamin K antagonist than the R-isomer. 2627 Clearance of S-isomer warfarin is inhibited by phenylbutazone, 2829 sulfinpyrazone, 30 metronidazole, 31 and trimethoprim- sulfamethoxazole, 32 each of which potentiates the effect of warfarin on the prothrombin time (PT). In contrast, drugs such as cimetidine and omeprazole that inhibit clearance of the R-isomer have only

moderate potentiating effects on the PT in patients treated with warfarin. 272833 Amiodarone inhibits the metabolic clearance of both the S-isomer and R-isomer and potentiates the anticoagulant effect of warfarin. 34 The anticoagulant effect is inhibited by barbiturates, 32 rifampicin, 34 and carbamazepine, 32 which increase its metabolic clearance by inducing hepatic mixed oxidase activity. Although long-term alcohol use has a potential to increase the clearance of warfarin through a similar mechanism, consumption of even relatively large amounts of wine was shown in one study²⁹ to have little influence on PT in subjects treated with warfarin. For a more thorough discussion of the effect of enzyme induction on warfarin therapy, the reader is referred to a critical review (Table 2). 35

The pharmacodynamics of warfarin are subject to genetic and environmental variability. Hereditary resistance to warfarin occurs in rats³⁶ as well as in human beings. 3738 Patients with genetic warfarin resistance require doses fivefold to 20-fold higher than average to achieve an anticoagulant effect. This disorder is attributed to altered affinity of the receptor for warfarin since the plasma warfarin levels required to achieve an anticoagulant effect are increased.

Two mis-sense mutations in the factor IX propeptide have been described³⁹⁴⁰⁴¹ that cause bleeding without excessive prolongation of PT. When affected individuals are treated with coumarin drugs, factor IX activity decreases to about 1 to 3%, while levels of other vitamin K-dependent coagulation factors decrease to 30 to 40% of normal. These mutations are uncommon and have been estimated to occur in < 1. 5% of the population. A plausible mechanism for the selective increase in coumarin sensitivity of the

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mutant factor IX proposed by Chu et al³⁹ reconciles the following observations: (1) normal factor IX activity in the absence of coumarin despite reduced binding of the variant propeptide to Γ^3 -carboxylase, and (2) marked suppression of factor IX activity by coumarin despite only modest suppression of the other three vitamin K-dependent coagulation factors.

Subjects receiving long-term warfarin therapy are sensitive to fluctuating levels of dietary vitamin K, ^{42,43} which is provided predominantly by phylloquinone in plant material. ⁴³ The phylloquinone content of a wide range of foodstuffs has been listed by Sadowski and associates. ⁴⁴ Phylloquinone acts through the warfarin-insensitive reductase reaction. ⁴⁵ Important fluctuations in vitamin K intake occur in both apparently healthy and sick subjects. ⁴⁶ Increased intake of dietary vitamin K sufficient to reduce the anticoagulant response to warfarin⁴² occurs in patients on weight-reduction diets consuming green vegetables or receiving vitamin K-containing supplements, and in patients treated with IV supplements containing vitamin K. Reduced dietary vitamin K¹ intake potentiates the effect of warfarin in sick patients treated with antibiotics and IV fluids without vitamin K supplementation and in states of fat malabsorption. Hepatic dysfunction potentiates the response to warfarin through impaired synthesis of coagulation factors. Hypermetabolic states produced by fever or hyperthyroidism increase warfarin responsiveness, probably by increasing the catabolism of vitamin K-dependent coagulation factors. ^{47,48} Drugs may influence the pharmacodynamics of warfarin by inhibiting synthesis or increasing clearance of vitamin K-dependent coagulation factors or by interfering with other pathways of hemostasis (Table 3). The anticoagulant

effect of warfarin is augmented by the second-generation and third-generation cephalosporins, which inhibit the cyclic interconversion of vitamin K, 4950 by thyroxine, which increases the metabolism of coagulation factors, 48 and by clofibrate, through an unknown mechanism. 51 Doses⁵² of salicylates > 1.5 g/d also augment the anticoagulant effect of warfarin, 54 possibly because these drugs have warfarin-like activity. Acetaminophen has also been reported to augment the anticoagulant effect of warfarin, 52 although this contention has been challenged (see below). Although heparin potentiates the anticoagulant effect of warfarin, in therapeutic doses, it produces only slight prolongation of the PT.

Drugs such as aspirin, 55 nonsteroidal anti-inflammatory drugs, 56 high doses of penicillins, 5758 and moxolactam⁵⁰ increase the risk of warfarin-associated bleeding by inhibiting platelet function. Of these, aspirin is the most important because of its widespread use and prolonged effect. 59 Aspirin and nonsteroidal anti-inflammatory drugs can also produce gastric erosions that increase the risk of upper-GI bleeding. 58 The risk of clinically important bleeding is heightened when high doses of aspirin are taken in combination with high-intensity warfarin therapy (INR, 3.0 to 4.5). 5560 In two studies, one study⁶¹ in patients with prosthetic heart valves and the other study⁶² in asymptomatic individuals at high risk of coronary artery disease, low doses of aspirin (100 mg/d and 75 mg/d, respectively) were also associated with increased rates of minor bleeding when combined with moderate-intensity and low-intensity warfarin anticoagulation.

The mechanisms by which erythromycin⁶³ and some anabolic steroids⁶⁴ potentiate the anticoagulant effect of warfarin are unknown. Sulfonamides

and several broad-spectrum antibiotic compounds may augment the anticoagulant effect of warfarin by eliminating bacterial flora and aggravating vitamin K deficiency in patients whose diet is deficient of vitamin K. 65

Wells and associates⁶⁶ performed a critical analysis of articles reporting possible interaction between drugs or foods and warfarin. Studies were assigned to one category if the interaction was considered highly probable, to a second category if interaction was probable, to a third level if judged possible, and to a fourth level if doubtful. Of 751 citations retrieved, pertinent results from 172 original articles are summarized in Table 3. Strong evidence of interaction was found for 39 of the 81 different drugs and foods appraised; 17 potentiate warfarin effect, 10 inhibit, and 12 produce no effect. Many other drugs have been reported to either interact with oral anticoagulants or alter the PT response to warfarin, ⁶⁷68 but convincing evidence of a causal association is lacking. In a case-control study, 52 low to moderate doses of acetaminophen (nine or more tablets per week) were reported to be associated with excessively prolonged INR values. The presence of a causal association between acetaminophen use and potentiation of a warfarin effect is uncertain. The article⁵² was supported by an editorial, ⁵³ but has been challenged by personal experiences (case series) cited in two letters⁶⁹⁷⁰ and by the results of a prospective study⁷¹ in normal volunteers. However, until more information is presented, it would be prudent to monitor the INR more frequently when acetaminophen is used in this quantity by patients during warfarin therapy. Indeed, it would be reasonable to monitor the PT more frequently when any drug therapy is

added or withdrawn from the regimen of a patient treated with an oral anticoagulant.

DRUG INTERACTIONS: Your doctor or pharmacist may already be aware of any possible drug interactions and may be monitoring you for them. Do not start, stop, or change the dosage of any drug, vitamin, or herbal product without checking with your doctor or pharmacist first. Warfarin interacts with many prescription, nonprescription, vitamin, and herbal products. This includes medications that are applied to the skin or inside the vagina or rectum. The following interactions listed do not contain all possible drug interactions. The interactions with warfarin usually result in an increase or decrease in the “ blood-thinning” (anticoagulant) effect. Your doctor or other health care professional should closely monitor you to prevent serious bleeding or clotting problems. While taking warfarin, it is very important to tell your doctor or pharmacist of any changes in medications, vitamins, or herbal products that you are taking. This drug should not be used with the following medications because very serious interactions may occur: imatinib, mifepristone. If you are currently using any of these medications listed above, tell your doctor or pharmacist before starting warfarin. Aspirin and aspirin-like drugs (salicylates) and nonsteroidal anti-inflammatory drugs (NSAIDs such as ibuprofen, naproxen, celecoxib) may have effects similar to warfarin. These drugs may increase the risk of bleeding problems if taken during treatment with warfarin. Carefully check all prescription/nonprescription product labels (including drugs applied to the skin such as pain-relieving creams) since the products may contain NSAIDs or salicylates. Talk to your doctor about using a different medication (such as

acetaminophen) to treat pain/fever. Low-dose aspirin and related drugs (such as clopidogrel, ticlopidine) should be continued if prescribed by your doctor for specific medical reasons such as heart attack or stroke prevention. Consult your doctor or pharmacist for more details. Many herbal medications have “ blood-thinning” or “ blood-clotting” effects, and some may directly affect warfarin. Tell your doctor before taking any herbal products, especially bromelains, coenzyme Q10, cranberry, danshen, dong quai, fenugreek, garlic, ginkgo biloba, ginseng, goldenseal, and St. John’s wort, among others. This medication may interfere with a certain laboratory test to measure theophylline levels, possibly causing false test results. Make sure laboratory personnel and all your doctors know you use this drug. This document does not contain all possible interactions. Therefore, before using this product, tell your doctor or pharmacist of all the products you use. Keep a list of all your medications with you, and share the list with your doctor and pharmacist