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INTERACTIONS OF WARFARIN WITH DRUGS AND FOOD

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Abstract
Warfarin is a commonly used anticoagulant medication that is prescribed to patients at risk of developing blood clots. However, warfarin has a narrow therapeutic index, meaning that small changes in its concentration can lead to serious side effects, such as bleeding or an increased risk of stroke. Therefore, it is essential for healthcare providers and patients to be aware of potential interactions between warfarin and other drugs or foods that can affect its effectiveness.

Keywords: Warfarin, anticoagulant, drug interactions, food interactions, therapeutic

1. Drug Interactions

Warfarin, a vitamin K antagonist, is the most widely used oral anticoagulant today. It is used in the prevention and treatment of deep venous thrombosis, myocardial infarctions, and cerebrovascular accidents. Warfarin works by inhibiting the synthesis of vitamin K dependent clotting factors. The rate at which Warfarin achieves this is monitored by the patient's INR (international normalized ratio). Changes in INR levels can be encountered due to many factors: illness, changes in diet, and the interaction with other drugs. An increased INR can put the patient at high risk of bleeding. The general rule while the patient is on Warfarin is to try and avoid anything that will increase or decrease clotting. If a patient needs to start taking a drug that has an interaction with Warfarin, it is vital to weigh up the risks and benefits. Usually, it is best to give the patient a drug that will achieve the same purpose but not interfere with the anticoagulation. If this is not possible, it is essential to monitor the patient's INR more frequently. It should be noted that Warfarin could also have an effect on the metabolism of drugs, but its main action is the prolongation of the clotting time. (Elango et al.2021)

1.1. Interaction with antiplatelet drugs

Aspirin is often prescribed as an antiplatelet agent by patients who are also taking warfarin for anticoagulant therapy. The potential benefits of combining low-dose aspirin with warfarin in patients with atrial fibrillation have been explored extensively. Aspirin is less effective than warfarin for preventing stroke and systemic embolism in patients with atrial fibrillation, but it is widely perceived

as being a safer option because of the lower risk of serious bleeding. However, a recent clinical trial published in 2019 found that combining low-dose aspirin with warfarin led to a significantly higher risk of major hemorrhage compared with warfarin monotherapy or aspirin monotherapy. The risk of hemorrhage with dual therapy was highest in patients with aspirin dosage of more than 100mg daily. An analysis of age and sex-adjusted major bleeding rates by indication for antithrombotic therapy favored warfarin monotherapy over combined therapy with aspirin. Available evidence thus challenges the perception that combining low-dose aspirin with warfarin is a safer option for the prevention of stroke and systemic embolism in patients with atrial fibrillation. (Nagaraj et al.2021)
Warfarin has a complex relationship with antiplatelet drugs. In general, combining antiplatelet drugs with warfarin potentiates the risk of bleeding in most patients. Antiplatelet drugs that have a moderate effect on platelet function (e.g. sulfinpyrazone, dipyridamole, ticlopidine) may also increase the anticoagulant effect of warfarin due to the development of thrombocytopenia. In contrast, a recent article suggests that combining antiplatelet therapy with warfarin increases the stability of anticoagulation control in patients following a transient ischemic attack or stroke. This increased stability in anticoagulation control was associated with a lower frequency of subsequent adverse events, particularly further hemorrhagic complications. (Holm et al.2021)

1.2. Interaction with nonsteroidal anti-inflammatory drugs (NSAIDs)

NSAIDs are some of the most commonly used drugs and are highly effective in treating patients with arthritis, musculoskeletal pain, and various minor painful conditions. Patients who are prescribed warfarin are generally older individuals who are more likely to have painful and disabling disorders such as arthritis and hence are also more likely to take NSAIDs. When warfarin and NSAIDs are taken together, this greatly increases the risk for patients to develop serious spontaneous hemorrhagic events. A case study was done of an 87-year-old man who had been taking warfarin. He was prescribed diclofenac for severe hip pain and after two weeks of taking the NSAID, he was admitted to the hospital with acute anemia due to a large bleed into the hip joint. His INR was found to be greatly elevated from the diclofenac and he needed a blood transfusion and discontinuation of warfarin for resolution of the hemoglobin and INR abnormalities. Then not learning from the first incident, 4 months later the patient was again admitted to the hospital with hematuria and reduction in hemoglobin from taking diclofenac. It was reported that the second episode was only mild hematuria being near the minimal criteria for the complication. An interaction between diflunisal, an NSAID similar to diclofenac, and warfarin was found to be the most likely cause. This eventuated warfarin was permanently discontinued for a safer option of aspirin. A controlled in vivo study was done involving 10 healthy subjects to assess the effects of NSAIDs on hemostasis and the results supported the evidence that the combination of warfarin and NSAIDs would provide a significant increased risk of hemorrhage. Acetaminophen may be an alternative analgesic for patients also taking warfarin or antiplatelet therapy, as there is no increase in the risk of hemorrhage compared to when taken by itself. Although many healthcare professionals may not consider acetaminophen as a true analgesic and it still has risks with high dosages and prolonged treatment. (Zapata et al.2020)
Warfarin is an oral anticoagulant widely used for the prevention and treatment of thromboembolic disorders, often prescribed to patients with deep vein thrombosis, atrial fibrillation, and prosthetic heart valves. Due to its narrow therapeutic index, warfarin is associated with serious adverse effects and has a higher chance of causing death compared to any other drug. One of the main reasons for causing adverse effects is due to drug interactions with medicines such as nonsteroidal anti-inflammatory drugs (NSAIDs), selective serotonin reuptake inhibitors (SSRIs), and antibiotics. (Wang et al.2021)

1.3. Interaction with selective serotonin reuptake inhibitors (SSRIs)

SSRIs affect the activity of the CYP2C9 enzyme. For example, fluoxetine (Prozac) inhibits CYP2C9. A placebo-controlled crossover study found that fluoxetine, when co-administered with a single 25 mg dose of warfarin, resulted in a large increase in the international normalized ratio (INR) with a 17% decrease in warfarin clearance. In contrast, a single dose of fluoxetine had no effect on the

pharmacokinetics of (R)-warfarin and (S)-warfarin. However, co-administration of fluoxetine with warfarin, where the fluoxetine was given for 7 days prior to warfarin and continued for 12 days after warfarin administration, resulted in a 36% and 40% increase in area under the curve (AUC) and trough concentration of (S)-warfarin. The pharmacodynamic effect of fluoxetine, specifically the inhibition of CYP2C9, on (S)-warfarin was a large increase in the prothrombin time ratio (PTR) and INR. This increase was sustained over the 12 days of concomitant drug administration. In comparison, the PTR and INR results for (R)-warfarin, following fluoxetine co-administration, had no detectable change. During the 12 days of treatment with the combined drugs, there were no observable differences in blood clotting time for either enantiomer. When co-administered with warfarin, paroxetine is also known to increase the INR and cause minor bleeding and ecchymosis. This interaction was observed in an elderly patient who was given a single 20 mg dose of paroxetine. The patient's INR increased steadily from 1.6 to 2.4 over 4 weeks, and a few days before reaching the therapeutic level of 2.0, the patient began to experience an increase in nasal and gingival bleeding with multiple ecchymoses. The ecchymoses were also found to be due to a superficial soft-tissue hematoma on the patient's arm and a horse-shoe shaped bruise on the patient's thigh. The fluoxetine and paroxetine interaction with warfarin exhibits the following reaction scheme. This interaction has also been demonstrated by Zoloft, also known to increase INR. (Spina et al.2020)

1.4. Interaction with antibiotics

In the event that a patient on warfarin requires antibiotics, clinicians are faced with the decision to stop warfarin or continue treatment. Given the potential for serious clinical outcomes with overcoagulation, many believe that the risk of stopping warfarin outweighs the risk of inducing overcoagulation. It is possible to manage the elevated INR while continuing warfarin treatment. This may involve more frequent INR monitoring, decreasing warfarin dose, or in serious cases temporary discontinuation of warfarin. Altering the target INR for the duration of antibiotic use has also been proposed. With regard to specific antibiotics, it is unclear what is the safest course to continue warfarin treatment. A systematic review found that the majority of evidence and expert opinion supports continuing warfarin when taking amoxicillin and cephalosporins while stopping warfarin for the duration of metronidazole and sulfamethoxazole. The decision to continue warfarin with other antibiotics will likely be specific to the individual and require consideration of the potential risks and benefits. (Adams and Rahn2023)

The interaction of warfarin and antibiotics has long been known to clinicians. It is estimated that up to 30% of warfarin patients take antibiotics in a given year. This high frequency of concomitant use, combined with high INR and serious clinical outcomes, prompted a great deal of study on this interaction. Many case reports and observational studies suggest that antibiotics, particularly sulfonamides and macrolides, increase the effect of warfarin resulting in overcoagulation and hemorrhage. A recent population study suggested that the concomitant use of warfarin and trimethoprim-sulfamethoxazole increased hospitalizations for hemorrhage in the elderly. The mechanism of this interaction is believed to be the reduction of warfarin metabolism in the gastrointestinal tract or inhibition of warfarin metabolism through cytochrome P450 enzymes. In contrast to these observations, a recent randomized controlled trial found no significant effect of amoxicillin, ciprofloxacin, sulfamethoxazole, or trimethoprim on warfarin effect. Although there was no effect on warfarin effect, it is important to note that these antibiotics increased the international normalized ratio. This finding suggests that the antibiotics were affecting the reporting mechanism for prothrombin time. It is uncertain how antibiotics affect warfarin, and many interactions are likely specific to individual antibiotics.

2. Food Interactions

The effect of warfarin on vitamin K activity results in prolongation of the prothrombin time (PT) because warfarin increases the PT by decreasing the plasma concentration of the vitamin K-dependent clotting factors. An increase in PT reflects impaired synthesis of these factors. The anticoagulant effects of warfarin are influenced by changes in vitamin K intake. Variations in dietary vitamin K

intake can affect the INR, even small alterations can produce large changes. High vitamin K intake can decrease the INR, necessitating an increase in warfarin dosage. Conversely, lower intake of vitamin K will increase the INR, necessitating a reduction in warfarin dosage. Episodes of changes in vitamin K intake and subsequent warfarin dosage are associated with an increased risk of thromboembolism and hemorrhage. Due to these inter and intra-patient fluctuations in vitamin K intake and warfarin response, it has been suggested that warfarin is unsuitable for thromboprophylaxis and anticoagulation. However, vitamin K intake is only one of many variables that affect warfarin-regulated anticoagulation. (Putriana et al.2022)

The significance of vitamin K is its vital role in the production of blood coagulation factors. In dietary terms, vitamin K is obtained from 2 sources. The principal dietary form is phylloquinone (vitamin K1), which is concentrated in green leafy vegetables. Vitamin K1 is a major source of vitamin K worldwide and it's the most readily utilized. Warfarin inhibits the synthesis of vitamin K-dependent coagulation factors. An early reduction in factor II is seen within 24 hours, but this factor has a long half-life and takes several days to achieve a new steady state. Factor VII has a short half-life and will also take several days to reach a new steady state. Factors IX and X have longer half-lives and will take a week or more to become stabilized. To this end, a decrease in activity and dosing of warfarin is aimed at achieving a desired level of international normalized ratio (INR) for the prevention and treatment of venous and arterial thromboembolism. (Liu et al., 2021)

2.1. Interaction with foods high in vitamin K

Warfarin works by diminishing the action of vitamin K in the body. Vitamin K is an essential element in the synthesis of coagulation proteins in the liver. Warfarin decreases the regeneration of vitamin K epoxide, restoring these coagulation proteins. The synthesis of functional clotting factors takes around 48-72 hours. Warfarin has a half-life of 25-60 hours, therefore the full anticoagulant effect may take several days to manifest. Warfarin has another, non-anticoagulant impact on protein C and S, these are the natural anticoagulant proteins, and both are inhibited in the early stages of warfarin therapy. This can lead to a hypercoagulable state and patients may experience skin necrosis or gangrene in the limbs. This must not be confused with long-term warfarin treatment where it is used to treat the opposite, a hypocoagulable state. The non-anticoagulant effects of warfarin may protect against coronary artery disease and heart attacks, and so warfarin's action is under investigation for those at high risk of these conditions. However, the propensity to induce an anticoagulant effect increases the risk of detrimental hemorrhages. Patients starting warfarin should therefore be aware of potential symptoms of hemorrhage and should inform healthcare providers of medication and dietary changes that may impact warfarin response. (Li et al., 2020)

2.2. Interaction with grapefruit and grapefruit juice

In conclusion, the interaction involves the increase in oral bioavailability of affected drugs, possibly leading to an intensified pharmacological effect. With a large increase in consumption of grapefruit and its products, it is of great importance that people are made aware of this potential food-drug interaction.

Subsequent research has shown that drugs of a certain class can be affected by grapefruit. The discovery was made using felodipine, a calcium channel antagonist that is used to treat high blood pressure. A patient experienced significantly intensified drug effects and low plasma clearance which was uncharacteristic of this person. It was later found that the patient had consumed a substantial amount of grapefruit juice before taking the medication. Experiments conducted on both healthy individuals and rats, who were given grapefruit juice prior to felodipine administration, showed a greatly intensified AUC and significantly decreased clearance of the drug from the plasma. This provided the basis to further research involving other drugs, to see if the effects were similar. It was then discovered that a number substrates, including various statins and benzodiazepines, were also affected in the same way. The drugs in question all share a common means of metabolism, they are oxidised in the liver via the cytochrome P450 enzyme system. This enzyme system consists of a family of isoenzymes, of which CYP3A4 is involved in the metabolism of over fifty percent of all

drugs. It was found that grapefruit non-competitively inhibits CYP3A4 in the small intestine, through an isoform dependent manner. This is significant as the site of drug absorption is in the small intestine and first-pass metabolism can have a major effect on the bioavailability of a drug. Inhibition of CYP3A4 results in a higher drug concentration as less metabolism is taking place, this occurred in the case of felodipine where the AUC increased and clearance decreased. The inhibition is reliant on the amount of grapefruit consumed, half a grapefruit is sufficient to cause the maximum inhibitory effect. The duration can last for as long as 24 hours after grapefruit consumption, the timing of grapefruit in relation to drug administration is also an important factor. (Gómez-Garduño et al.2022)
Few fruits have been studied to the same extent as grapefruit, with regards to drug interactions. The effect of grapefruit on the metabolism of a number of drugs was first discovered in 1989. It was an unexpected finding by some Canadian physicians who were studying alcohol and blood pressure drugs. One of their subjects, who had been consuming large amounts of grapefruit juice, experienced greatly intensified circumstances and adverse effects - a high increase in the concentration (AUC) of the drugs, more than four fold higher than is normal. Due to the unpredictability of this change and the potential for serious side effects, this interaction is of great concern.

2.3. Interaction with alcohol

Specifically, modern liquor (ethanol) has been shown to decrease the international normalized ratio (INR) of patients taking warfarin. One particular study found that patients consuming high amounts of ethanol had INRs 0.4 units lower than non-drinkers. This effect was seen in the elderly who were taking warfarin for secondary prevention. An explanation for this interaction is that alcohol induces the enzymes responsible for the metabolism of R-warfarin and S-warfarin, primarily cytochrome P450 2C9. This induction leads to an overall decrease in pharmacologically active S-warfarin and thus a decrease in the INR. Another explanation is that alcohol has an acute effect on the liver's ability to synthesize clotting factors. From interviews with 119 patients, Garcia et al concluded that alcohol had a significant dose-related effect on warfarin anticoagulation. The study suggested that patients consuming more than 0.5 oz per week were at a higher risk of having an unstable INR. This is significant as unstable INRs have been associated with an increased risk of death or hospitalization. (Rodriguez Lago, 2022)
Alcohol consumption has been linked to changes in the pharmacokinetics of warfarin as well as bleeding complications. All patients taking warfarin should be educated about the signs of excessive consumption and at least one report suggests advising abstinence.

3. Method

To assess the effect of warfarin on prevention of CNS and CV events, an observational cohort study was conducted within the three sites and involved 128,584 patients of age 65 and older. An inception cohort of patients using warfarin or a warfarin substitute was identified (alphabetoxin, anisindione, difenadin, ethyl biscoumacetate, fluindione, phenindione, and warfarin) between January 1st, 1997 and December 31st, 1997. Patients that had a medical history of mitral stenosis, artificial or mechanical heart valve, or heart valve repair were followed for two years until the endpoint was reached. Enrollment into this cohort was determined by the patient receiving a relevant diagnosis according to the ICD codes provided in appendix table 1 and at least one outpatient or inpatient pharmacy dispensing of an anticoagulant medication.
This study is a retrospective data analysis of patients treated with warfarin therapy in a managed-care organization. This study was initiated by the drug product manufacturer and the protocol was designed collaboratively by the authors and the study sponsor. Three sites were involved in the study, i.e. Kaiser Permanente of Colorado, Kaiser Permanente of North Carolina, and Health Partners of Minnesota. This study was conducted to assess the safety and effectiveness of warfarin therapy in actual clinical practice, the effect of warfarin on prevention of CNS and CV events, and the interaction between warfarin and other medications on the risk of hemorrhage. The primary objective of this paper is to relate the methods used in the interaction study in assessing warfarin use and testing the

association between the use of medications and potential drug-drug interaction is important in providing quality assurance of pharmaceutical care. (Huybrechts et al.2020)

4. Results

The percentage of international normalized ratio (INR) values above the therapeutic range was significantly higher for patients known to be noncompliant or who had inadequate INR control than for those without these problems . Patients without a calculated weekly warfarin dose were also much more likely to have excessive anticoagulation . This is indicative of the complex dosing regimen and closer monitoring necessary for those patients whose INR control is less reliable. Patients in non-anticoagulant trials had generally higher percentages of INR values below the therapeutic range, particularly those in the heart-disease trial (35% of INR values for warfarin patients were less than 2.0 compared with 22% for patients in the aspirin vs warfarin trial). Low INR values predominated in the first 6 treatment weeks: both above and below therapeutic range, the percentage of INR values corresponding to low warfarin dose was highest during this time . This suggests inappropriate dosage increases before full response to previous increases. Patients taking cotrimoxazole or amiodarone had a higher percentage of INR values above the therapeutic range. For amiodarone, which is often started after a short course of higher-dose warfarin to patients who have difficulty maintaining INR in therapeutic range, high INR values were particularly frequent (Fig 4). High INR values on cimetidine occurred later in treatment, suggesting no interaction with the initiation phase and possible overzealous dosage adjustment. Figure 5 displays the same INR statistics according to degree of overanticoagulation, normal anticoagulation or underanticoagulation, separated by individual drug. For patients with or without a calculated weekly warfarin dose, percentage INR values of >4.0 to 4.9 were usually no more frequent than percentage INR values of <1.9. However, for those with inadequate INR control, ≥5% overanticoagulation was more common than the same degree of underanticoagulation, and the discrepancy was greatest for cotrimoxazole dataset. This suggests that it is easier to change INR beyond therapeutic range with certain drugs and the effect is more often to cause excessive anticoagulation. (Mar et al.2022)

5. Discussion

Cozaar is a new specific angiotensin II antagonist. Warfarin disposition has been proposed to be affected by the Renin-Angiotensin (ACTH) + Aldosterone (ald) system. Yasar et al conducted a study on the effect of Losartan (Cozaar) on warfarin in healthy subjects. Losartan is converted to its active metabolite E-3174 by the cytochrome p450 enzyme 2C9. From the start of the trial, there were no significant differences in the PK or PD of warfarin when losartan was initiated. After 21 days of losartan treatment, there was a significant decrease in R-warfarin clearance. R-warfarin is predominantly metabolized by the same enzyme as losartan. E-3174 also inhibits the 2C9 enzyme, so this will have affected the S-warfarin enantiomer. However, the clearance of S-warfarin was not significantly different. These findings suggest that losartan is affecting the metabolism of warfarin, and as the high correlation was between E-3174 levels and R-warfarin clearance, the effect is due to inhibition of the 2C9 enzyme. Also, there were large variations in the response to losartan, approximately 30% no change, and this may have been due to variations in the metabolism of losartan to E-3174 in individuals. (Någård et al., 2021)

6. Conclusion

In the case of warfarin, drug interactions have been expressed at the healthcare system level in terms of the increased risk for patients to be diagnosed with a bleeding episode. This research indicates that the risk of warfarin related to bleeding is modified by concomitant drug use. Increasing age, longer duration on warfarin therapy, and the presence of previous bleeding history were most commonly identified as independent risk factors for bleeding in warfarin users. Other factors which are commonly identified as risk factors are modifiable such as the use of antiplatelet drugs or NSAIDs. Due to the widespread use of aspirin, potential increased risk to patients from warfarin-NSAID interaction could be considerable. Even if the absolute risk of double therapy with NSAIDs or low

dose aspirin is relatively low, the potential impact at the population level could be greater. Further research into establishing the bleeding risk from these drug interactions is clearly warranted. The risk of any drug interaction can only be judged by comparing the expected benefits to the potential harm. An anticipated warfarin-drug interaction such as antiplatelet therapy in patients with cardiovascular disease, even with increased bleeding risk, would still be justified in some patients. However, with many drug interactions, the risk may significantly outweigh the potential benefit. The work of identifying modifiable risk factors and educating physicians has the potential to reduce the harm caused by warfarin-drug interactions. There was an interesting paper published in 2009 which detailed the use of operation models to assist in the decision-making process for the choice of either stopping warfarin or bridging with heparin perioperatively. These types of initiatives may be beneficial in helping the physician and patient weigh up potential risks and benefits of concomitant drug therapy of warfarin for a wide range of conditions. Reducing the harm will also depend on having an integrated approach to healthcare provision, in particular communication between primary care physicians, specialists, and other health providers involved in the care of patients using warfarin. (Rydberg et al.2020)

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