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Review Article

**CONCOMITANT USE OF NON-STEROIDAL ANTI-  
INFLAMMATORY DRUGS (NSAIDS) WITH WARFARIN**

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**Abstract:**

**Introduction:** Oral anticoagulation with warfarin is the accepted technique for treatment and prophylaxis of thromboembolic diseases. Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most broadly administered medications to control musculoskeletal pain or inflammation. Besides to their antiplatelet work, NSAIDs can influence the pharmacologic activity of warfarin through their immediate interaction. High protein binding and the cytochrome P450 (CYP)- dependent clearance systems of NSAIDs can influence the serum levels of warfarin.

**Aim of work:** In this review, we will discuss whether using warfarin with NSAID has any effect on the pharmacokinetics and pharmacodynamics of both drugs.

**Methodology:** We conducted this review using a comprehensive search of MEDLINE, PubMed, and EMBASE, January 1985, through February 2017. The following search terms were used: Non-steroidal anti-inflammatory drug mechanism, warfarin mechanism, adverse effects of NSAID, adverse effect of warfarin, NSAID-warfarin interaction

**Conclusions:** Co-administration of NSAIDs and Warfarin is a topic of debate. However, there are reasons for concern. Some NSAIDs alter hemostasis and, when combined with warfarin, may lead to an increase in bleeding time. There is also a risk of increased hepatic and renal toxicity which complicates things further. Balancing the pros and cons of this drug combination should be carefully done on a case to case basis to avoid any negative consequences.

**Key words:** NSAID, warfarin, Aspirin, drug-drug interaction, bleeding

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**INTRODUCTION:**

Oral anticoagulation with warfarin is the accepted technique for treatment and prophylaxis of thromboembolic diseases. While the adequacy of warfarin on anticoagulation is well known, it can cause a conceivably lethal complication, hemorrhage. Hemorrhage appear almost as much as 9.6% of patients every year, including a deadly case rate of 0.6% [1].

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most broadly administered medications to control musculoskeletal pain or inflammation. Besides to their antiplatelet work, NSAIDs can influence the pharmacologic activity of warfarin through their immediate interaction. High protein binding and the cytochrome P450 (CYP)- dependent clearance systems of NSAIDs can influence the serum levels of warfarin. Therefore, there have been many case reports depicting bleeding complications after NSAIDs were given alongside warfarin [2].

The level of anticoagulation with warfarin is typically checked with international normalized ratio (INR), which is a solid indicator of future bleeding risk; every one-point elevation in INR builds bleeding risk by 54.0%. Hence, checking INR is essential when prescribing warfarin. In this regard, stopping NSAIDs or changing warfarin dose ought to be considered if INR increases after adding NSAID [3].

**METHODOLOGY:****• Data Sources and Search terms**

We conducted this review using a comprehensive search of MEDLINE, PubMed, and EMBASE, January 1985, through February 2017. The following search terms were used:

**• Data Extraction**

Two reviewers have independently reviewed the studies, abstracted data, and disagreements were resolved by consensus. Studies were evaluated for quality and a review protocol was followed throughout.

The study was approved by the ethical board of King Abdulaziz University Hospital

**NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS):****Mechanism of Action**

The significant therapeutic actions of NSAIDs are fundamentally enacted by their capacity to block

certain prostaglandins (PGs) synthesis through the cyclooxygenase enzymes (COX-1 and COX-2) inhibition. COX-1 produces prostaglandins and thromboxane A<sub>2</sub> which control mucosal barrier in GI-tract, renal homeostasis, platelet aggregation and other physiological functions. COX-2 produces PGs that related to inflammation, pain and fever. COX-1 is expressed in normal cells, while COX-2 is induced in inflammatory cells. COX-2 inhibition no definitely represents the desired effect of NSAIDs' anti-inflammatory, antipyretic and analgesic reaction; while COX-1 inhibition plays a great role in the complications such as GI and renal toxicities [2].

Most NSAIDs are readily absorbed in the gastrointestinal system and have high bioavailability. A few medications, for example, diclofenac undergo hepatic first-pass metabolism which led to a decrease in bioavailability. While other medications such as sulindac and parecoxib are prodrugs and need hepatic metabolism to become their active metabolites (sulindac sulfide and valdecoxib, respectively). NSAIDs are profoundly bound to plasma proteins. NSAIDs are typically metabolized in the liver and excreted through the kidney. Commonly administered NSAIDs medications have a variable half-life; they can be around the range of 0.25-0.3 hours such as aspirin or 45-50 hours such as piroxicam. All these pharmacokinetics parameters can be altered with age since the elderly have low body water compared to adults. Protein binding might be diminished, and volumes of distribution might be changed [4].

**Gastrointestinal Adverse Effects**

The injury of gastric and duodenal mucosa caused by NSAIDs has been significantly evaluated. These upper GI reactions include bothersome manifestations with or without mucosal damage, asymptomatic mucosal lesions, and drastic complications, including death.

Around 30 to 50% of NSAID consumers have endoscopic lesions, (such as subepithelial hemorrhages, erosions, and ulcerations), majorly situated in gastric antrum, and frequently without clinical appearances. commonly, these lesions have no clinical importance and lessen or even vanish with prolonged use, most likely due to the adaptation of mucosal layer to aggression. In contrast, up to 40% of NSAIDs consumers have upper GI side effects, commonly being gastroesophageal reflux (regurgitation and/or heartburn) and dyspeptic manifestations (includes belching, epigastric discomfort, bloating, early satiety and postprandial

nausea) [5]. The beginning of these side effects appears to fluctuate depending upon the type of NSAID. A meta-analysis of the available trials from the Cochrane collaboration presumed that COX-2 selective inhibitor (celecoxib) was related with less symptomatic ulcers, endoscopically identified ulcers and cessations for GI adverse events compared with ns-NSAIDs (naproxen, diclofenac, ibuprofen and loxoprofen). regrettably, these side effects are not predictive of the presence of mucosal damage. Roughly 50% of individuals with side effects have no mucosal lesions; however, >50% of consumers with drastic peptic ulcer complications had no previous warning manifestations [6].

The most critical upper GI complications are the event of symptomatic and/or complicated peptic ulcer. NSAID-related upper GI side effects include bleeding, perforation and obstruction. Around 1 to 2% of NSAID consumers encountered a drastic complication amid treatment. Case-control trials and a meta-analysis have demonstrated that the average relative risk (RR) of creating uncomplicated or complicated peptic ulcer is fourfold and fivefold in NSAIDs consumers compared with non-consumers. The risk is recommended to be higher amid the first month of treatment (RR, 5.7; 95% confidence interval CI, 4.9 to 6.6), but stays raised amid administration and 2 months after stopping treatment [7].

## WARFARIN:

### Mechanism of Action

Warfarin's anticoagulant effects help halt clot development and the extension of any existing clots, yet it has no immediate impact on clot removal or reversing ischemic tissue injury. Warfarin shows its anticoagulation effects through the intrinsic and extrinsic pathways in the clotting cascade. This happens by inhibiting the synthesis of vitamin K-dependent clotting factors (II, VII, IX, and X) and the anticoagulant proteins C and S. Warfarin meddles with the synthesis of clotting factors by inhibiting the vitamin K oxidation-reduction cycle required for the carboxylation of clotting factors. This finally reduces the amount of active vitamin K reserves available to act as a cofactor in the development of glutamic acid residues inside the previously mentioned clotting factors [8].

Warfarin's hepatic metabolism and protein binding are the most widely recognized mechanisms for the event of drug-drug interactions. Warfarin is metabolized through cytochrome P450 system by 2C9, 1A2, and 3A4. It is a racemic mixture of R and

S enantiomers with the S-enantiomer being 2.7 to 3.8 times more intense than the R-enantiomer. Since the S enantiomer is more powerful and is principally used by CYP 2C9, drug-drug interactions effecting this pathway might be more remarkable. Drugs with a higher protein binding affinity than warfarin (e.g., aspirin) can displace warfarin creating further free warfarin inside the blood stream [9].

### Adverse Effects

Clinical manifestations of bleeding should be monitored upon initial administration of warfarin since this is the most common risk factor. infrequent yet serious adverse effects include tissue necrosis, calciphylaxis, and systemic atheroemboli and cholesterol microemboli. Tissue necrosis typically starts within days of initiating warfarin and has been related with individuals having deficiencies of proteins C or S. Warfarin lessens the synthesis of both of these normally occurring anticoagulant proteins. combined administration of heparin for 5 to 7 days may limit the frequency of necrosis when starting warfarin. Calciphylaxis was recently added as a warning to warfarin and can result in calciphylaxis or calcium uremic arteriopathy in patients with or without end-stage renal disease. systemic atheroemboli and cholesterol microemboli may occur because of the release of plaque emboli after the administration of warfarin. Different areas inside the body can be influenced including the feet. In particular, purple toe syndrome happens when microemboli travel to a patient's toes and may happen months after the initiation of warfarin. In the instances of all drastic adverse effects, alternative anticoagulation treatment ought to be considered unless the risk exceeds the advantage of taking an anticoagulant [10;11].

There are several drugs and herbal products that can potentiate or repress the effects of warfarin. Any drug that influences the capacity to clot, for instance, other anticoagulants, antiplatelets, nonsteroidal anti-inflammatory agents (NSAIDs), and selective serotonin reuptake inhibitors (SSRIs) will expand the risk of bleeding even when there is not a specific drug-drug interaction. Drug-drug interactions are various and more often lead to an elevation in PT/INR levels except if the associative medicine is a CYP P450 inducer such as rifampin [12].

### Concomitant use of Warfarin and NSAIDs

As a class, NSAIDs are not inclined to a direct pharmacodynamic interaction with anticoagulants, such as warfarin; nevertheless, simultaneous administration of NSAIDs and anti-thrombotics may

additionally enhance the probability of GI bleeding.<sup>82</sup> A Danish cohort study (N=4,204) found that anticoagulants alone elevate the risk of GI bleeding (standardized incidence ratio [SIR]: 4.0; 95% CI: 2.8– 5.6), and risk was additionally elevated by combined use of acetaminophen (SIR: 4.4; 95% CI: 1.2– 11.4) or non-aspirin NSAIDs (SIR: 8.0; 95% CI: 2.1– 20.4; no specific NSAIDs or doses reported) [13]. Metabolism of S-warfarin, the most clinically important warfarin isomer, happens by means of CYP2C9. Ibuprofen and different NSAIDs are also substrates of CYP2C9 and may in this manner elevate anticoagulant action by postponing S-warfarin metabolism. Therefore, it might be reasonable to evade prescription-strength NSAIDs in patients consuming warfarin. Conversely, one of the metabolites of acetaminophen (N-acetyl-para-benzoquinone-imine) interferes with enzymes involved with the vitamin K cycle, which eventually can prompt decrease in synthesis of clotting factors and excessive anticoagulation [14]. Even with short-term use, acetaminophen given simultaneously with anticoagulants may elevate international normalized ratio (INR), suggesting an increase in bleeding risk and requiring close INR monitoring and possible warfarin dosage adjustments [15].

Additionally, to having direct effects on warfarin, NSAIDs potentially increase the side effects of anticoagulants administered orally by two other mechanisms. ASA is known to influence primary hemostasis in some typical individuals by causing irreversible acetylation of cyclo-oxygenase in platelets, which results in a prolongation of the bleeding time. Alternate NSAIDs additionally influence platelet function yet generally in a reversible fashion, and their effects on bleeding time and bleeding tendency are less pronounced. In doses well over the therapeutic range ASA could also have a hypoprothrombonemic effect by diminishing the vitamin K-dependent clotting factors,' yet. this is rarely an issue in clinical practice [14].

It is also conceivable that the severity of gastrointestinal bleeding induced by ASA or other NSAIDs could be elevated by the combined use of anticoagulants. The role NSAIDs play in inducing acute upper gastrointestinal tract hemorrhage is as yet debatable, however the risk from normal ASA use has been estimated at no more than 15 episodes per 100 000 consumers for every year. The use of alcohol in individuals taking warfarin might be a more serious issue than this. One of the few studies to observe the complications of combined ASA and warfarin treatment found that the rate of gastrointestinal bleeding was increased over that seen

with warfarin alone. However, there was a high correlation among the prothrombin index and the frequency of bleeding, and the prothrombin index was quite often over the therapeutic levels. Almost all the episodes of gastrointestinal bleeding happened amid the first month of combined therapy [16].

There are two different purposes for caution. First, individual differences regarding these medications and their interactions do happen. ASA's ability to delay the bleeding time ranges from none in a few people to marked in others and has additionally been appeared to be dose and age-dependent. Second, patients taking warfarin and NSAIDs in combination may as well have renal or liver dysfunction or be taking still different other medications. Most trials on NSAID/warfarin interaction have included healthy volunteers. The potential for more complex interactions is therefore extraordinary [17].

### Mechanisms of Adverse Drug Interactions

#### Direct Hypo-prothrombinemic Effect of Aspirin

Aspirin and different other salicylates may have a hypo-prothrombinemic effect by depressing the vitamin K-dependent synthesis of clotting factors VII, IX, and X. nevertheless, such an activity just winds up critical if the equivalent exceeds 6 g (for a 70-kg man) of aspirin every day has been ingested." The PT is rarely prolonged except if the serum salicylate concentrations exceed of 300 mg/ml,," concentrations at which salicylate toxicity is more certainly [18].

#### Pharmacokinetic Mechanisms

Two main types of pharmacokinetic interactions have been reported: displacement of warfarin from plasma albumin and blockade of the metabolism of warfarin by NSAIDs. The role of protein binding displacement in interactions with warfarin has been overemphasized. Although most NSAIDs, which are extremely protein-bound, have been found to displace warfarin from plasma albumin binding zones in vitro, this interaction has only been shown in vivo with some NSAIDs [19].

Additionally, in vivo trials have demonstrated that this displacement does not importantly elevate the anticoagulant activity of warfarin. An elevation in the plasma concentration of unbound (pharmacologically active) warfarin following the administration of the displacing NSAID will be transient due to combining increase in the clearance of unbound warfarin until the previous concentration is hit. Therefore, displacement might be vital only for intermittent warfarin administration and on introduction and



withdrawal of the displacing NSAIDs. In such circumstances, the effect again is transient and steady-state ought to be reached after 7-10 days. A clinically important interaction also might be more likely in the presence of high concentrations of NSAIDs in individuals with slow elimination of warfarin (e.g., those with severe heart failure or impaired liver function) [20].

Phenylbutazone considerably inhibits the metabolism of S-warfarin while elevating the hepatic clearance of R-warfarin." The net outcome is increased anticoagulation without an adjustment in the overall clearance of racemic warfarin. It is likely that analogs of phenylbutazone (oxyphenbutazone, apazone, and sulfinpyrazone) will interact with warfarin in a similar manner. Same data for other NSAIDs are not available, as plasma concentrations of total warfarin as opposed to its isomers have been estimated in studies of interaction with warfarin [21].

### Pharmacodynamic Mechanisms

Two pharmacodynamic interactions have been reported: direct effects on platelets and producing upper gastrointestinal (GI) bleeding. Aspirin irreversibly acetylates platelet cyclooxygenase at low or high dosages and produces irreversible consequences for platelet function that persevere for the life of the aspirin-treated platelet." Platelet aggregation furthermore might be inhibited and the bleeding time delayed. Similarly, however usually lesser, consequences for platelet function might be seen with non-aspirin NSAIDs, yet unlike aspirin, these effects are lost when the medication or any active metabolites are removed from the circulation.' Therefore, the effects are typically reversible in 24 hours for short-acting NSAIDs, yet may proceed for many days longer-acting NSAIDs. Because of the side effects on hemostasis, NSAIDs increase the risk of bleeding from the GI tract or different other locations amid combined use [20].

Several studies have demonstrated that an individual exposed to NSAIDs has 3-4 times the risk of upper GI bleeding, perforation, or both than an individual who has not been exposed." An extensive variety of mechanisms could clarify the occurrence of NSAID-induced gastroduodenal mucosal injury, including the inhibition of bicarbonate secretion, effects on mucus development, and vascular actions. The individual risks are low, of the order of 1 episode for each 10,000 NSAID prescriptions issued to individuals aged 60 years and older in the UK. Due to numerous such prescriptions are issued, there are numerous episodes. In a study of patients with rheumatoid arthritis, the rate of hospitalization due to upper GI

bleeding in individuals taking NSAIDs was 1.58% every year compared with 0.3% in those not taking the agents." In addition to old age, other clinical variables of predictive value included use of prednisone, disability, the dose of NSAIDs, and past problems with NSAIDs. Upper GI bleeding is expected to be more notable in individuals taking warfarin [7].

### CONCLUSION:

Co-administration of NSAIDs and Warfarin is a topic of debate. However, there are reasons for concern. Some NSAIDs alter hemostasis and, when combined with warfarin, may lead to an increase in bleeding time. Upper GI bleeding can occur in patients taking NSAIDs which is further complicated when warfarin is added to the mix. There is also a risk of increased hepatic and renal toxicity which complicates things further. Balancing the pros and cons of this drug combination should be carefully done on a case to case basis to avoid any negative consequences. More studies should be conducted to clarify the implications of combining NSAIDs and warfarin.

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