## Warfarin and flax seed oil interaction and a mechanism for Polyunsaturated Fatty Acid and Warfarin interactions

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**Introduction:**

Warfarin is the most widely prescribed oral anticoagulant in North America and the 11th most prescribed drug in the United States[1]; however, it is underutilized in those who meet criteria for warfarin therapy due to concerns regarding bleeding complications. Warfarin therapy requires frequent monitoring via the International Normalized Ratio (INR) which places considerable time and financial burdens on our healthcare system. In addition, a plethora of genetic, food, drug and herbal interactions are associated with warfarin use. In a recent systematic review of warfarin interactions, 187 separate reports were investigated and only 14 were deemed 'highly probable' for potentiation of warfarin's effect on the INR. One of these 14, fish oil, has recently been touted as a valuable source of omega-3 polyunsaturated fatty acids (PUFAs). Recent data suggest that omega-3 PUFAs like those found in fish oil and flax seed oil (a plant source of omega- 3 PUFAs) play a protective role cardiovascular disease. Many patients with cardiovascular disease have the potential to receive concomitant warfarin and omega-3s. However, only interactions with warfarin and fish oil have been reported. We present the first such observed 'possible' interaction, as assessed by the Drug Interaction Probability Scale (DIPS), and propose a novel mechanism to explain the observed interaction in not only flax seed oil, but fish oil as well.

**Case report:**

A 55 year-old Hispanic female was initially admitted with shortness of breath and diagnosed with atrial fibrillation in June 2005. She was started on oral anticoagulation with warfarin. Her early warfarin course was complicated by intermittent vaginal bleeding for which warfarin was periodically held until 8/1/2007. During those two years, warfarin doses were adjusted at our primary care clinic and INR was never greater than 4.0.

She was recently admitted with systolic Heart Failure (HF) and chronic shortness of breath worse during the last week. Her past medical history includes hypertension, dyslipidemia, asthma, obesity, uterine fibroids, gastro-esophageal reflux disease, atrial fibrillation and stable systolic HF. Her medications at admission were lisinopril daily, carvedilol twice daily, furosemide daily, montelukast daily, albuterol inhaler as needed, prednisone as needed, rosuvastatin daily, esomeprazole daily and warfarin 6mg and 7mg alternating days.

She regularly follows up in clinic and her INR had been within therapeutic range (2-3) for the last three consecutive visits on her the above warfarin regimen. She was seen in clinic for a routine visit three days prior to admission and the INR was 2.8. On admission, the complete blood count, chemistry and liver function tests were all normal, BNP (brain natriuretic peptide) was 168pg/mL (below the patients previous range of 180-240) but the INR was markedly elevated to 4.60 (Figure 1). There were no recent changes in prescription medications, the patient is adherent with a low Vitamin K diet and there has been no recent alcohol or tobacco consumption. No other potentiating warfarin interactions were found. History of over-the-counter and herbals elicited the use of flax seed oil supplements for the past three days (*Nopalina* containing 2g of alpha-linolenic acid twice daily), starting immediately after the previous clinic visit. Warfarin was held for two days and then restarted at 3mg daily as an inpatient. Upon discharge, INR was 1.25, warfarin was increased to 6mg daily and the patient was instructed to discontinue flax seed oil

supplementation. One week after discharge, the INR was returned to a therapeutic level (2.4) on a dose of 6mg daily while the patient abstained from flax seed oil supplementation.

**Discussion**:

The list of reported interactions with warfarin continues to grow, but few have substantial evidence to support their validity. Many interactions lack a convincing mechanism, which perpetuates doubt and uncertainty surrounding these interactions. In the last few years, with the rise in popularity of omega-3 fatty acid supplementation, an increasing number of reports were published linking fish oil (docosahexaenoic acid (DHA) and eicosapentanaenoic acid (EPA)) to warfarin toxicity and even hemorrhage. Proposed theories included the anti-platelet effect of PUFAs, lipid alterations affecting vitamin K delivery to the liver and increased warfarin absorption. However, these theories are not supported by evidence. Anti-platelet effects cannot account for elevated INR. Although fish oil and flax seed oil have been shown to decrease triglyceride levels, multiple studies found no effect on clotting factor levels.[9] Absorption is unlikely to be an issue since warfarin's bioavailability is nearly 100%. Even though alpha-linolenic acid is a biological precursor of EPA and DHA, only ~10% of supplemental alpha-linolenic acid is converted to DHA and EPA.[10] Thus flax seed oil supplementation accounts only for a small rise in DHA and EPA levels, seemingly excluding a mechanism of interaction specific to fish oil.

New evidence supports a mechanism of omega-3 PUFA competitive inhibition of warfarin metabolism by P450 cytochrome enzymes. Warfarin is principally metabolized by CYP2C9.[11] Recent studies reveal that several PUFAs competitive inhibitors of CYP2C9, and alpha-linolenic acid, DHA, and EPA all have a Ki value of less than 5uM indicating potent inhibition of CYP2C9. Inhibition of warfarin metabolism may explain the observed omega-3 PUFA-warfarin interaction and, although not routinely done, could be further substantiated by measuring warfarin plasma levels in patients throughout a suspected course of interaction.

This mechanism of action is consistent with the observed interaction in our case. Flax seed oil supplementation may have decreased warfarin metabolism, allowing warfarin levels to rise resulting in a higher INR. Once flax seed oil was stopped, CYP2C9 activity returned to baseline with resumption in baseline warfarin requirements to maintain a therapeutic INR. We must acknowledge several limitations and potential confounders in our case. Our pt was admitted with HF which can cause decreased hepatic blood flow and decreased warfarin clearance. Serial BNP levels argue against acutely worsening heart failure. Rosuvastatin has been associated with increased INR, however, the patient in our case continued to take rosuvastatin before and after the interaction. Rechallenging the patient with flax seed oil may recreate the circumstances of the interaction, however, given the dangers of elevated INR, this approach has questionable ethical implications.

**Conclusion:**

While warfarin interactions with omega-3 PUFAs in fish oil have been observed, we present the first case of flax seed oil interaction with warfarin. Our case underscores the importance and difficulty in patient education and dietary compliance with patients on warfarin therapy. We also propose a mechanism that explains the entire PUFA class interaction with warfarin via direct inhibition of CYP2C9 metabolism of warfarin. Further reports and trials will likely be necessary to fully characterize the extent of this interaction.