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Fish Oils and Warfarin

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Background

An increased intake of oily fish and long-chain polyunsaturated omega-3 fatty acids (fish oils) is generally beneficial and reduces the risk of ischemic stroke. For people on warfarin it is clearly important to know if it is safe to take both fish oils and warfarin.

Warfarin works by inhibiting the activation of vitamin K-dependent coagulation Factors V, VII and X in the extrinsic and common pathways of the coagulation cascade. Fish oil works primarily by inhibiting platelet aggregation, stabilizing atherosclerotic plaque, and reducing fibrinogen level, but there is some evidence that it also reduces Factors V and VII in both men and women and Factor X in women.[1,2]

There is no evidence that fish oil causes hemorrhagic stroke or internal bleeding, while there is abundant evidence that warfarin does.[3-7] Warfarin was originally developed as a rat poison and has two effects – it damages the integrity of blood vessel walls and inhibits the normal blood clotting action which would prevent the rat from bleeding to death. It would seem that a similar mechanism operates in humans.

The purpose of anticoagulants like warfarin and fish oil is to prevent blood from forming a clot or at least significantly increase the length of time it takes before a clot is formed in response to trauma or stagnation. There are several different tests for measuring clotting tendency, and it is somewhat unfortunate that the test in general use today, the prothrombin time (INR), is not an absolute measure of the blood's tendency to form a clot (thrombus), but rather a measure of the blood level of those coagulation factors that depend on vitamin K for their synthesis and the factors they, in turn, activate. In other words, the universal test today is primarily designed to measure blood level of warfarin. Aspirin, vitamin E, garlic and other natural antiplatelet/anticoagulant agents generally have no or very little effect on INR – and yet, these substances all have proven preventive effects against thrombus formation.

The problem is that the INR test only measures blood coagulation time in the extrinsic and common pathways. Retardation of the coagulation sequence by antiplatelet aggregation medications (aspirin, clopidogrel, ticlopidine), for example, will not affect INR because the sequence is halted in the intrinsic pathway before vitamin K-dependent coagulation factors become involved. Similarly, if the coagulation process is initiated via the intrinsic pathway and prekallikrein, Factor VIII or von Willebrand Factor are blocked, the thrombus formation sequence

will not proceed either, but the INR test, because it bypasses the intrinsic pathway, will not show that you are protected even though you clearly are.

It is clear that both fish oil and warfarin are effective anticoagulants and it is thus likely that taking both would be superior to either agent alone in preventing ischemic stroke. The question is, "Would taking both increase the risk of hemorrhagic stroke and internal bleeding?" As far as I know only three studies have investigated the possible interaction between warfarin and fish oil.

Clinical Studies

A group of Norwegian medical researchers found that fish oil supplementation did not increase the bleeding tendency in heart disease patients receiving aspirin or warfarin. The study involved 511 patients who had undergone coronary artery bypass surgery. On the second day after the operation half the patients were assigned in a random fashion to receive 4 grams of fish oil per day (providing 2 g/day of eicosapentaenoic acid, 1.3 g/day of docosahexaenoic acid, and 14.8 mg/day of vitamin E). At the same time the patients were also randomized to receive either 300 mg of aspirin per day or warfarin aimed at achieving an INR of 2.5-4.2. The patients were evaluated every 3 months and questioned about bleeding episodes for the duration of the 9-month study.

The researchers concluded that fish oil supplementation did not result in a statistically significant increase in bleeding episodes in either the aspirin group or in the warfarin group. Nosebleeds were somewhat more common in the fish oil + warfarin group, while gastrointestinal bleeding was more common in the warfarin group. None of the differences were statistically significant. They also found no significant long-term effects of fish oil on common parameters of coagulation and fibrinolysis – including bleeding time. They noted that the blood levels (serum phospholipid levels) of eicosapentaenoic acid and docosahexaenoic acid increased by 140% and 14% respectively in the patients taking fish oil. The serum triglyceride levels decreased by 19.1% in the fish oil group while no significant change was observed in the remainder of the patients.[8]

Researchers at the University of Texas Health Sciences Center have addressed the question, "Does fish oil supplementation change INR in patients on warfarin?" Their placebo-controlled, randomized, double-blind study included 11 patients with prosthetic heart valves, cardiomyopathy or deep vein thrombosis who were taking warfarin and had achieved stable INR values for at least 4 weeks. The participants were assigned to receive a placebo, 3 grams/day of fish oil (*MaxEPA*), or 6 grams/day of fish oil for a 4-week period. Their INR was measured twice weekly during the study period. INR values remained steady in all groups and there were no significant differences in INR values between the groups during the trial. The researchers conclude that, "there does not appear to be a clinically significant interaction between warfarin and up to 6 grams/day of the fish oil supplement *MaxEPA* in terms of INR changes and bleeding incidence." [9]

Mitchell Buckley and colleagues at the Shawnee Mission Medical Center in Kansas recently reported the case of a 67-year-old woman whose INR increased significantly after she increased her daily dose of fish oil from 1 gram to 2 grams. The woman had serious health problems (TIAs, hypothyroidism, hyperlipemia, osteopenia, and coronary artery disease) and had experienced a heart attack necessitating angioplasty. She was taking several medications including warfarin, aspirin, levothyroxine, atorvastatin, bisoprolol, lisinopril, and conjugated estrogens. She was also supplementing with 400 IU a day of vitamin E and 1 gram a day of fish oil. The patient had been stable for a 5-month period at an INR of between 2 and 3 taking 1.5 mg a day of warfarin. In March 2002 she increased her fish oil dosage to 2 grams a day and a week later her INR measured 4.1. Upon returning to 1 gram a day of fish oil her INR dropped to 1.6. The researchers conclude that the higher dose of fish oil could have provided additional

anticoagulation as expressed in a higher INR. There was no indication that the INR was affected by 1 gram a day of fish oil.[10]

Conclusion

There is no evidence that taking both warfarin and fish oil increases the incidence of bleeding. However, there is no clear consensus as to whether fish oil affects INR. One small study found that 3 and 6 grams a day of fish oil had no significant effect on INR, whereas a single case study found that 2 grams a day increased INR significantly. Thus, it would appear that supplementing with 1 gram a day of fish oil while on warfarin is safe and does not affect INR.

It is not clear whether higher fish oil intakes may affect INR, so it is advisable to increase INR monitoring frequency when changing one's daily fish oil intake. It is possible, but certainly not proven, that taking fish oil and warfarin together may reduce the amount of warfarin required to keep the INR in the therapeutic range.

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