CASE STUDY

Omega-3 Fatty Acid Supplementation and Warfarin: A Lethal Combination in Traumatic Brain Injury

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ABSTRACT

Polyunsaturated fatty acids such as omega-3 eicosapentaenoic acid and omega-6 docosahexaenoic acid, found in over-the-counter fish oil supplements, are often consumed for their beneficial, prophylactic, anti-inflammatory effects. Although the mechanisms of action are not fully known, a diet rich in polyunsaturated fats may reduce the risk of hyperlipidemia, atherosclerosis, high low-density lipoprotein cholesterol levels, hypertension, and inflammatory diseases. Masked by its many benefits, the risks of omega-3 fatty acid supplementation are often underappreciated, particularly its ability to inhibit platelet aggregation and promote bleeding in patients taking anticoagulant medications. The following details the clinical case of an elderly patient taking warfarin and fish oil supplementation whose warfarin-induced coagulopathy could not be reversed after suffering blunt head trauma.

Key Words

Bleeding risk, Fish oil, Omega-3 fatty acid, Warfarin

Although commonly consumed for its anti-inflammatory benefits (Wall, Ross, Fitzgerald, & Stanton, 2010), numerous case studies have detailed the potentially harmful antithrombotic effects of omega-3 fatty acid supplementation in inhibiting platelet aggregation and promoting bleeding (Buckley, Goff, & Knapp, 2004; Dyerberg, 1981; Jalili & Dehpour, 2007; McClaskey, 2007; Stranger, Thompson, Young, & Lieberman, 2012). One particular population at increased risk for such complications include those concurrently taking anticoagulation medications such as warfarin, as the combination of substances can greatly increase a patient's bleeding risk (Dyerberg, 1981; Mayo Clinic, 2013). In 2004, Buckley et al. reported the case of a 67-year-old woman taking warfarin and omega-3 supplementation who experienced a 1.5-fold increase in international normalized ratio (INR), a measure of prothrombin time/clot formation, following an increase in her fish oil dosage. Similarly, Jalili and Dehpour (2007) reported the case of a 65-year-old man taking warfarin whose INR reached 8.06 after beginning a fish oil regimen for undefined complaints. Both patients' INR returned to normal following the discontinuation of fish oil supplementation (Buckley et al., 2004; Jalili & Dehpour, 2007). The interaction between warfarin and the omega-3 fatty acids of the fish oil supplement was proposed as the plausible cause in both cases.

The authors were only able to locate one clinically relevant case in the literature that detailed a 75-year-old patient on high-dose omega-3 fatty acid supplementation and warfarin who experienced bleeding complications after suffering fall-induced head trauma (McClaskey, 2007). Eventually requiring neurosurgical intervention, the authors hypothesized that omega-3 fatty acid supplementation was at the root of the patient's increased bleeding propensity.

CASE REPORT

An 83-year-old man presented to the emergency department with blunt head trauma status post motor vehicle collision (MVC). Upon admission, the patient had a Glasgow Coma Scale (GCS) score of 14, was hypotensive and tachycardic, and suffered from respiratory distress. An airway assessment revealed a possible blood aspiration resulting from the drainage of a large lip laceration, leading to his immediate intubation. Following stabilization in the trauma bay, the patient received a preliminary computed tomographic (CT) scan that showed a small left subdural hematoma measuring 4-mm maximum thickness with no additional intracranial abnormalities (Figure 1A). The patient had a history of coronary artery disease, atrial fibrillation, dementia, and hypertension, for which his medications prior to admission included quetiapine,

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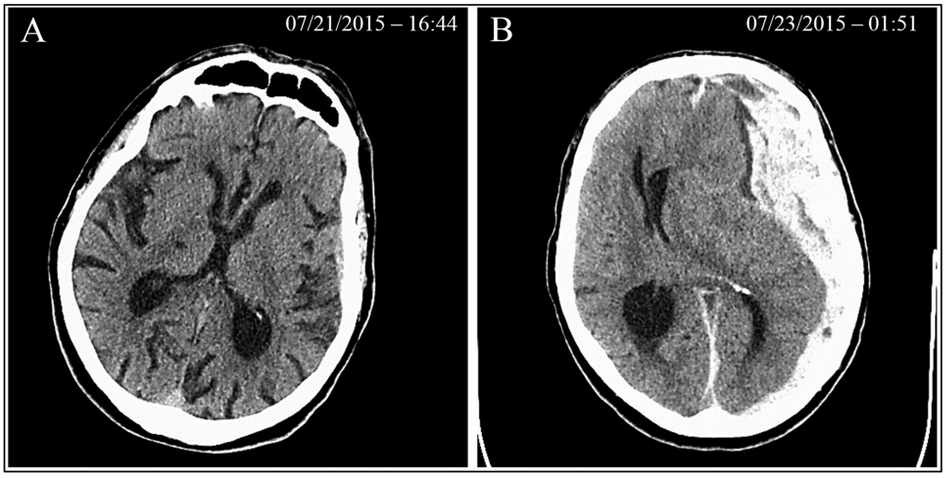

Figure 1. (A, B) Progression of patient's left-sided subdural hematoma over the course of 2-day stay.

docusate sodium, donepezil, levothyroxine, metoprolol, simvastatin, and, of special interest, omega-3 fatty acid fish oil supplements and warfarin.

Upon presentation, the patient had an elevated INR of 2.8. To reverse warfarin-induced coagulopathy, 35 international units per kilogram body weight of prothrombin complex concentrate (PCC) was given, along with 10 mg of intravenous vitamin K. Thirty minutes after PCC and vitamin K administration, the patient's INR reduced to 1.9 and a second dose of PCC was given. Following the administration of the second PCC treatment, the patient's INR increased to 2.4, and later to 3.0, confirming active coagulopathy. Two units of fresh frozen plasma (FFP) were transfused, and thromboelastography evaluation was conducted, which showed persistence in the warfarin-induced coagulopathy, platelet dysfunction, and factor deficiencies (Table 1).

A repeat CT scan the following day showed progression of the hematoma, now involving the left frontal, temporal, and parietal regions of the brain with a maximum depth of 2 cm. A new right frontal extra-axial hematoma was also detected. Along with the hematomas, diffuse edema within the left cerebral hemisphere, a 2-cm left-to-right midline shift, and an uncal and subfalcine herniation were noted. The lateral and third ventricles were subsequently compressed. Because of these findings, an additional 4 units of FFP were administered, along with a six pack of platelets and a five-pack pool of cryoprecipitate. Despite efforts to reverse coagulopathy, the patient's INR remained supratherapeutic and another repeat head CT scan showed further progression of the hematoma, which increased from 2-cm maximal thickness (most recent CT scan) to 3.9 cm (Figure 1B). In addition, the small right extra-axial hematoma increased from 1 to 5 mm and cerebral edema extended into the right hemisphere. Because of the patient's INR, he was not a candidate for neurosurgical intervention.

Throughout his 2.5-day stay, the patient showed signs of steady neurological deterioration, with his initial GCS score of 14 reducing to a 7 within the first 24 hr, and ultimately a 3. Because of the inability to reverse the warfarin-induced coagulopathy, a craniotomy could not be performed to evacuate the massive, growing subdural hematoma. A central line was placed, and comfort care was provided until the patient expired later that evening.

DISCUSSION

The presented patient's condition was exacerbated by the inability to reverse warfarin-induced coagulopathy, which ultimately posed a contraindication for potentially life-saving neurosurgical intervention. Although it cannot be definitively confirmed, the patient's daily omega-3 supplementation likely contributed to this reversal issue. The Mayo Clinic (2013) cautions that interactions between omega-3 fatty acids and blood thinners can be particularly evident when the dose of omega-3 is higher than 3,000 mg per day. With fish oil capsules ranging from 300 to more than 1,000 mg, it is possible that the patient approached or exceeded this potentially dangerous level.

The normal clotting process is initiated by damaged endothelial tissues, which induce a signaling cascade that leads to platelet aggregation (Adams & Bird, 2009; King, 2016). The exposed collagen due to endothelial damage leads to the activation of phospholipase A_2, a hydrolytic enzyme that cleaves membrane phospholipids to free arachidonic acid. Arachidonic acid, an omega-6 fatty acid, increases the amount of thromboxane A_2, a vasoconstrictor and platelet activator. Once a platelet is activated, it will release adenosine diphosphate, which subsequently activates thromboxane A_2, leading to further platelet aggregation.

TABLE 1 Progression of Patient's Coagulopathy During Hospital Stay

	Time on Day 1				Time on Day 2					Time on Day 3	
	16:10	18:44	21:40	22:50	00:20	04:12	07:38	11:06	14:31	01:30	05:10
INR	2.8	1.9	2.4	3.0		2.2	1.6	1.4	1.3		1.4
TEG split point	5.6				9.3		6.7	6.8	6.4	5.6	4.9
TEG R value	5.9				11.8		7.6	7.8	7.2	6.1	5.3
TEG K value	1.8						4.9	5.3	2.6	2.3	2.0
TEG angle	67.4				14.6		40.8	38.6	56.2	63.7	63.7
TEG MA	68.2				19.4		47.3	51.1	58.9	62.4	62.4
TEG G	10.7				1.2		4.5	5.2	7.2	8.3	8.3
TEG Lysis 30	0				0		0	0	0	0.4	0.4
TEG A MA	11.6				2.1		2.7	3.3	6.6	12.2	12.2
TEG CFF MA									12.2	20.1	20.1
TEG ADP MA	57.5				2.1		2.1	3.4	6.7	41.3	41.3
TEG ADP G	6.8				0.1		0.1	0.2	0.4	3.5	3.5
TEG ADP% inhibition	18.9				100		100	99.8	99.8	42.0	42.0
TEG AA MA	52.2				19.4		32.6	28.2	39.5	49.7	49.7
TEG AA G	5.5				1.2		2.4	2.0	3.3	4.9	4.9
TEG AA% inhibition	28.3						33.0	47.9	37.1	25.3	25.3

Note. INR = international normalized ratio; TEG = thromboelastography.

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Warfarin is a widely prescribed anticoagulant. In 2004, more than 30 million prescriptions were administered for warfarin in the United States (Klein et al., 2009). Acting as a vitamin K antagonist, warfarin interferes with the cyclic conversion of vitamin K, which is required for posttranslational carboxylation of γ-carboxyglutamate residues of which coagulation Factors II, VII, IX, and X depend on. Warfarin, and other anticoagulants, interferes with the cyclic conversion of vitamin K, subsequently lowering the hepatic production of carboxylated proteins, resulting in partially carboxylated/decarboxylated proteins with reduced coagulation abilities (Hirsh et al., 2001).

As evidenced by this report, as well as previous case studies completed on the topic, much remains unknown regarding the synergistic antithrombotic effects of anticoagulant medications and omega-3 fatty acid supplementation. Although this is the first case study, to the authors' knowledge, that such a combination of substances resulted in patient death, multiple studies have reported similar omega-3 fatty acid-induced difficulties (Buckley et al., 2004; Jalili & Dehpour, 2007), one of which resulted in clinically relevant complications (McClaskey, 2007).

Similar to the approach taken to manage the aforementioned case, McClaskey (2007) employed aggressive treatment to reverse the warfarin-induced coagulopathy—likely exacerbated by high-dose fish oil supplementation—in the case of a 75-year-old fall victim. Presenting with an INR of 3.2, following administration of 4 units of FFP and a 5-mg dose of vitamin K, the patient's INR decreased to 1.6 in 2.5 hr and 1.2 in 15 hr. Per the recommendation of neurosurgery, 2 additional units of FFP were perfused to maintain an INR below 1.5 before performing a right frontoparietotemporal craniotomy for the evacuation of the patient's subdural hematoma. Although this management approach was successful in this case, similar aggressive management proved ineffective for our 83-year-old MVC victim.

CONCLUSION

Omega-3 and omega-6 fatty acids are essential fats that are commonly supplemented for their beneficial anti-inflammatory effects. Like warfarin, omega-3 fatty acids have an antithrombotic effect, which may place patients at an increased risk for bleeding. It is likely the interaction between the omega-3 fatty acids in the aforementioned patient's fish oil supplement and warfarin resulted in the inability to reverse supratherapeutic INR levels. Future management of patients concurrently taking warfarin and omega-3 fatty acids should focus on aggressive treatment measures to reverse coagulopathy. Nurses, physicians, and pharmacists must remain judicious when considering the potential antithrombotic effects

of combination therapy including anticoagulant medications and supplements.

KEY POINTS

- Omega-3 fatty acids found in fish oil supplements may have an antithrombotic effect, similar to that of warfarin and other anticoagulants.
- Combining omega-3 fatty acid supplements with anticoagulation medication may place patients at increased risk for bleeding.
- Physicians and pharmacists must remain judicious when considering the potential antithrombotic effects of combination therapy including anticoagulant medications and supplements.

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