Overdose of Anticoagulants in Patients Treated with Vitamin K Antagonists and Using Evening Primrose Oil: A Clinical Case and Theoretical Explanation

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Overdose of anticoagulant, VKAs, EPO, GLA

ABSTRACT:
This report presents the patient had an overdose of anticoagulants due to consuming evening primrose oil (EPO) while taking vitamin K antagonists (VKAs) in the patient has persistent atrial fibrillation, hypertension and heart valve problems. They were hospitalized, treated with vitamin K, and recovered. EPO has many health benefits, but it is necessary to avoid using EPO containing Gamma Linolenic Acid (GLA) fatty acid for patients who are using vitamin K antagonist (VKA) anticoagulants, as it can easily cause overdose anticoagulation, complications of bleeding, and endanger the patient's life.

INTRODUCTION

Vitamin K antagonists (VKAs), commonly used drugs like Acenocoumarol or Coumadin, are primarily used in the prevention of complications, stroke, and death in patients with atrial fibrillation. Typically, patients with atrial fibrillation without mechanical valves and no history of cerebral hemorrhage are prescribed VKAs with an International Normalized Ratio (INR) target of 2.0-3.0. Overdose of anticoagulants is a dangerous condition leading to bleeding due to abnormal blood clotting. This can be caused by protein deficiencies in the blood, abnormal protein function, lack of clotting factors, or abnormal clotting factors. [1,2,3]

Evening Primrose Oil (EPO) is a plant oil extracted from the seeds of Oenothera biennis L. Also known as EPO, it has yellow flowers that bloom and wither in the same evening. Originally from North America, it has naturalized in the Mediterranean region since its introduction to Europe in 1619 and is now widespread in Europe and parts of Asia. Historically, Native Americans used the seeds, roots, and leaves of evening primrose for various medicinal purposes, including wound healing and skin irritation. English herbalist John Parkinson (1567-1650) described the use of evening primrose in 1629. [4-9]

Evening primrose oil, EPO © Steven Foster [5]

Evening Primrose Oil: Benefits, Side Effects, and Interaction with Anticoagulants. This precious oil is known as one of the best functional foods, rich in vitamins, antioxidants, and high levels of essential fatty acids, primarily omega-6, including Linoleic acid (LA) accounting for 70-74% and Gamma Linolenic acid (GLA) accounting for 8-10%, a small amount of Dihomo-gamma linolein acid (DGLA), and Arachidonic acid (AA). [4-9] The therapeutic benefits of EPO mainly come from GLA, which, when absorbed into the body, produces a series of prostaglandins (PG), unsaturated fatty acids in tissues, acting as chemical mediators of inflammation and pain perception. Additionally, they have physiological effects on specific tissues, present everywhere in the body, with a wide range of physiological effects, acting like a tissue hormone.[10-15] GLA acts as an anti-inflammatory compound, supporting treatment, reducing swelling and inflammatory pain, softening the skin, reducing peeling, soothing and healing wounds, actively supporting the treatment of some skin diseases, causing vasodilation, facial redness, headaches, and potentially lowering blood pressure and balancing blood clotting. [16, 17,18]

However, if the body is incompatible, EPO can cause allergic reactions. Other side effects include stomach pain, abdominal pain, nausea, headache, dizziness, low blood pressure, and increased risk of bleeding, especially if you are taking anticoagulant medications, as EPO can interact and increase the risk of bleeding. [10-15]. However, there are few specific reports and clear explanations of this interaction in clinical practice involving people who are taking vitamin K antagonist (VKA) anticoagulants while simultaneously using EPO-derived functional foods. [13] Therefore, we report a case of atrial fibrillation being treated with VKA anticoagulants who were found to be using EPO-derived functional foods with bleeding disorders to share experiences and explain this issue based on world literature.

CLINICAL CASE REPORT

A 74-year-old female patient visited the hospital for a regular check-up in February 2023 with symptoms of gum bleeding. Medical history includes chronic atrial fibrillation, mitral regurgitation grade 2/4, aortic regurgitation grade 2/4, and tricuspid regurgitation grade 3/4, all of which were being stably managed. The patient was prescribed VKAs due to atrial fibrillation with a target INR of 2.0-3.0. Medical history revealed the patient was using a dietary supplement containing Evening Primrose Oil (1000mg/capsule) for about half a month. At that time, physical examination showed a heart rate of 77 beats/minute, blood pressure of 116/68 mmHg. The patient was also being stably treated with blood pressure medications Amlodipin+Perindopril 8/5 mg, Spironolacton 25 mg, Trimetazidin 35 mg, Atorvastatin, beta-blocker Metoprolol 25 mg, and anticoagulant Acenocoumarol at a stable dose of ½ tablet/day. Blood tests at that time showed an INR of 8.89 while other blood counts were within normal limits.

The patient was subsequently diagnosed with anticoagulant overdose due to the dietary supplement against the background of atrial fibrillation, hypertension, left atrial enlargement, aortic regurgitation grade 2/4, mitral regurgitation grade 1/4, tricuspid regurgitation grade 3/4, coronary artery disease, and fatty liver. The patient refused hospitalization and was treated for anticoagulant overdose by stopping the anticoagulant for 2 days. Clinical condition stabilized, and on the third day, the INR was 1.19. The patient was then continued on Acenocoumarol at a stable dose of ½ tablet/day with a warning not to continue using the aforementioned dietary supplement.

Following the procedure, the patient continued to comply with regular monthly follow-up visits. The INR index reached the treatment target for six consecutive months with a stable dose of Acenocoumarol at ½ tablet/day. Adjustments were rarely needed, with occasional doses of ¼ tablet/day on odd days and alternating with ½ tablet/day on even days.

In August 2023, although not yet due for a follow-up appointment, the patient was hospitalized due to symptoms of coughing up blood, bleeding gums, and nosebleeds. Physical examination showed the patient was alert, cooperative, with a heart rate of 68 beats/minute, blood pressure of 120/66 mmHg, SpO2 of 97%, and was being stably treated with maintenance medications including

Amlodipin+Perindopril 7/5 mg, Spironolacton 25 mg x 2 tablets/day, Trimetazidin 35 mg x 2 tablets/day, Atorvastatin 1 tablet/day, beta-blocker Metoprolol 50 mg x 1 tablet/day, and anticoagulant Acenocoumarol (Sintrom) at a stable dose of ½ tablet/day. The International Normalized Ratio (INR) index was stable within the therapeutic range for the past six months. Upon further medical history, it was discovered that due to curiosity, the patient had self-administered a functional food containing EPO (1300 mg/tablet) for 20 days with a regimen of 2 tablets/day. Basic biochemistry and blood tests were within normal limits, but the coagulation disorder index test this time showed an INR of 12.42.

Patient management: The patient was immediately hospitalized in the emergency department, anticoagulant medication was stopped for 2 consecutive days, and a single intravenous dose of 10 mg Vitamin K was administered. After treatment, the patient stabilized with an INR test on the second day showing an INR of 1.10. INR tests continued to be performed regularly once a month. The patient was warned not to use foods containing evening primrose oil while taking VKA anticoagulants.

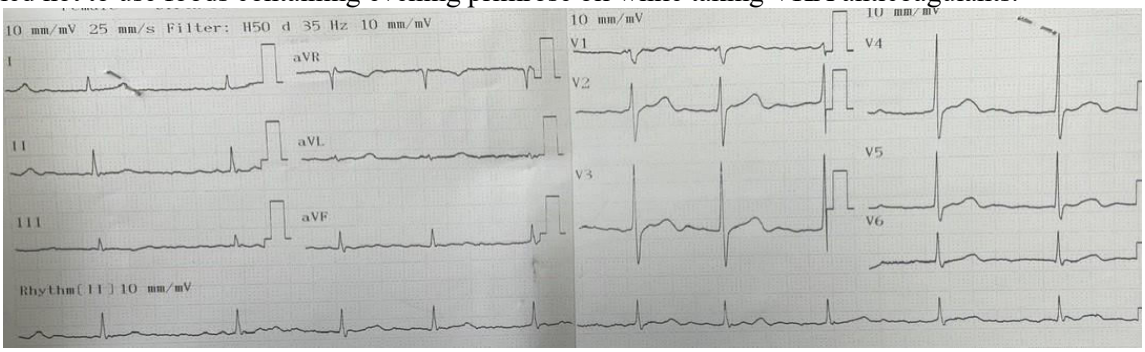

Figure 1 - Electrocardiogram 2/2023: Persistent atrial fibrillation, heart rate 62 beats/minute, normal axis, controlled ventricular rate 62 beats/minute, normal axis.

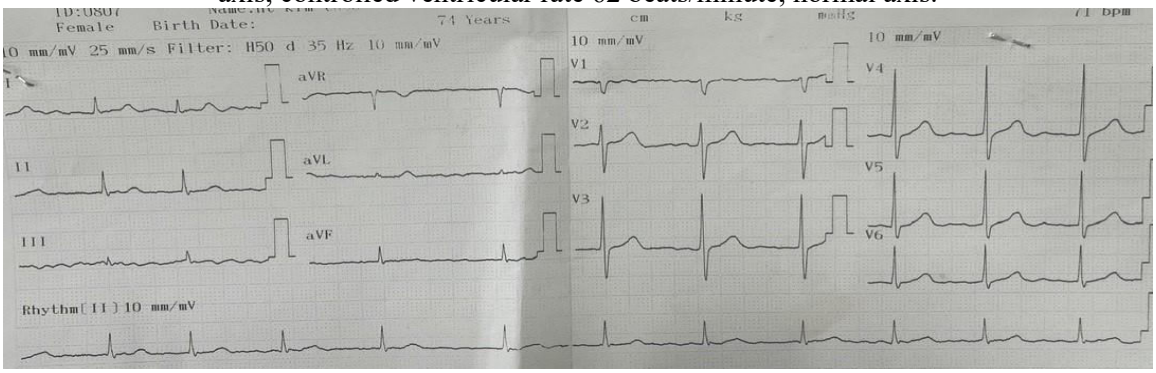

Figure 2 - Electrocardiogram 8/2023: Persistent atrial fibrillation, heart rate 71 beats/minute, normal axis, controlled ventricular rate 62 beats/minute, normal axis.

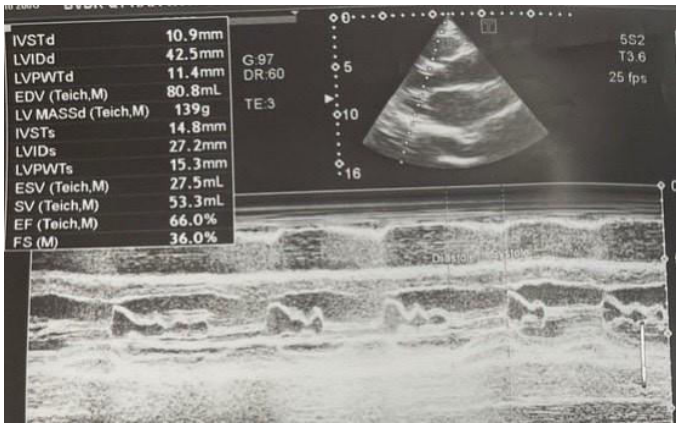

Figure 3 - Echocardiogram Doppler 8/2023: Left ventricular ejection fraction (EF): 66%, Mitral regurgitation grade 2/4, aortic regurgitation grade 2/4, tricuspid regurgitation grade 3/4.

DISCUSSION

Evening Primrose Oil (1000mg or 1300mg) is a product extracted from evening primrose oil, providing abundant omega-6 fatty acids and one of the best sources of gamma-linolenic acid (GLA). This acid helps balance female reproductive hormones, supports healthy skin, moisturizes the skin, reduces dry skin, reduces the risk of atherosclerosis, protects cardiovascular health, and protects overall health. The product is suitable for even those on diets. [10-15]

Evening Primrose Oil 1000mg or 1300mg, each capsule contains Omega 6 (involved in the construction of structures such as hormones, cell membranes, vitamin absorption, supporting transport, and numerous other metabolic processes) and Gamma-Linoleic Acid (GLA) acts as a necessary solvent for transporting fat-soluble vitamins like A, D, E, K, and also plays a role in converting carotene into vitamin A, enhancing mineral absorption, and participating in many other processes). Typically, evening primrose oil is used orally in clinical trials at doses of 1 to 8g/day for adults and 2 to 4g/day for children. The typical content of gamma-linolenic acid (GLA) inevening primrose oil is 8% to 10%. The treatment duration with evening primrose oil is usually between 3 and 12 months. [10, 16-18]

In this case, the patient used the recommended dosage for adults with 2 capsules/time/day, which is also the permitted dosage, not an excessive dose for adults. [10, 17] However, due to drug interactions, it led to an overdose of anticoagulant medication. We treated the overdose of VKA anticoagulants according to the recommendations of the American College of Chest Physicians.

Management of Anticoagulation with Vitamin K Antagonists

If INR ≥ 5 but < 9 and the patient has no significant bleeding: Stop the next 1-2 doses, check INR more frequently, and restart the medication at an adjusted dose when INR decreases to the therapeutic level. If the patient has a high risk of bleeding, one dose of the drug can be stopped and the patient can be given 1-2.5 mg of vitamin K. [1,2,3]

If INR ≥ 9 and the patient has no significant bleeding: Stop the vitamin K antagonist and give the patient 2.5-5 mg of vitamin K. INR usually decreases significantly after 24-48 hours. Check INR regularly, give additional vitamin K if necessary, and restart the medication at an adjusted dose when INR decreases to the therapeutic level. [1,2,3]

If the patient has severe bleeding and a high INR ≥ 9: Stop the VKA, inject 10 mg of vitamin K intravenously, and transfuse fresh frozen plasma, concentrated prothrombin complex, or recombinant factor VIIa. [1,2,3]

In general, EPO is relatively safe when used for a short period of time, but its long-term safety has not been established. Some studies have shown that EPO can cause problems for people with certain health conditions, including those with bleeding disorders, and can increase the effects of anticoagulants or antiplatelet drugs, thus increasing the risk of bleeding. This can be explained as follows:
The blood clotting process occurs through the intrinsic and extrinsic coagulation pathways, which converge at the common coagulation pathway with the activation of coagulation factor X (a vitamin K-dependent glycoprotein synthesized in the liver). This factor is responsible for converting prothrombin to thrombin. Thrombin stimulates the formation of fibrin (factor Ia) from fibrinogen (factor I), which has a hemostatic function at the site of injury. [19-23]
VKAs have an anticoagulant effect by reducing the production of vitamin K-dependent clotting factors from the liver (Factor II - Prothrombin, Factor VII - Proaccelerin, Factor IX - Antihemophilic B, and Factor X - Stuart). When the clotting factors are reduced, the extrinsic coagulation pathway is impaired, leading to increased anticoagulant effect. [19-23]

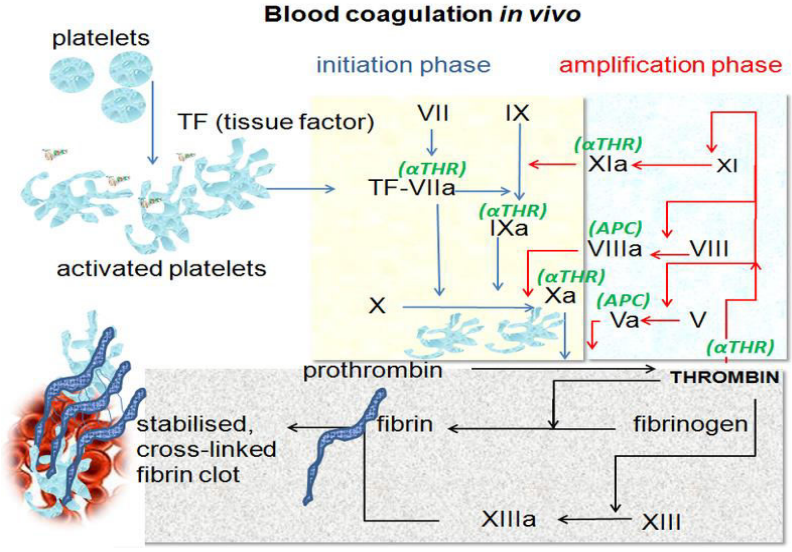

Figure 4 - Diagram: The blood clotting process in the body shows the central role of thrombin. [23]
According to the physiological mechanism, the g-carboxyglutamic acid (GLA) substance of blood clotting factors usually takes on the function of linking to phospholipid membranes, dependent on Ca ++, forming a Protein that binds factor X (X-bp), which is a special bond between factor X and the active substance GLA. Evening primrose oil contains components with GLAs. When introduced into the body, this structure also provides a binding model for factor X membrane to create X-bp (Protein linked to factor X), an anticoagulant protein, forming a special bond with the GLA region of factor X (a prefix of Xa). The formation of the complex can block the effective membrane interaction of the GLA active, limiting the conversion of prothrombin to thrombin, thereby limiting the production of Fibrinogen, which plays a role in hemostasis, leading to a reversal of the blood clotting/ hemostasis process at the injury site, causing bleeding disorders; This explains the mechanism of overdose anticoagulation that occurs in cases of using evening primrose oil in patients who are being treated with this VKAs anticoagulant. [19-25]
Through this mechanism, it can be clearly seen that the use of EPO containing GLA is a functional food that interacts with VKA anticoagulants, easily causing drug overdose, and should be noted to avoid using it in patients who are being treated with VKA anticoagulants. For cases without contraindications for

using EPO after consulting a doctor, Patients should still add EPO to their diet or drink gradually and stop using if there are any signs of side effects.

CONCLUSION

Through clinical cases and the above mechanistic explanations, it has been shown that EPO has many health benefits, but this functional food should not be abused to avoid unwanted side effects. Moreover, when taking EPO, you also need to observe the body's response to stop at the right time, limiting the possibility of adverse or dangerous conditions. Especially, it is necessary to avoid using EPO containing GLA fatty acid for patients who are using VKA anticoagulants, as it can easily cause overdose anticoagulation, complications of bleeding, and endanger the patient's life.

REFERENCES

1. Steffel J, Collins R, Antz M, et al. The 2021 European heart rhythm Association practical guide on the use of non – vitamin K antagonist oral anticoagulants in patients with atrial fibrillation: executive summary. *Europace*. 2023; 23 (10): 1612-1676.
2. Barbara S. Wiggins, Morgane Cibotti-Sun, Mykela M. Moore. 2023 Atrial Fibrillation Guideline at a Glance. *JACC* 2024; 83 (1): 280-284
3. Chu SD, Tran MT. Effect of Some Risk Factors on Over-Anticoagulation Disorder and Bleeding in Patients Receiving Anticoagulant Therapy with Overdosage of Vitamin K Antagonist. *Vascular Health and Risk Management.* 2023; 19 (Issue 2023): 663-672.
4. Sharon Chapman. Evening Primrose as a Carrier Oil. Sendona Aromatics. 2017. https://sedonaaromatics.com/an-introduction-to-evening-primrose-oil
5. Evening Primrose Oil. Office of Dietary Supplements (ODS), National Institutes of Health (NIH) 2020; https://www.nccih.nih.gov/health/evening-primrose-oil.
6. Vieira BL, Lim NR, Lohman ME, et al. Complementary and alternative medicine for atopic dermatitis: an evidence-based review. *American Journal of Clinical Dermatology.* 2016; 17 (6): 557-581.
7. R A Gibson , D R Lines, M A Neumann. Gamma linolenic acid (GLA) content of encapsulated evening primrose oil products. *Lipids.* 1992 Jan; 27 (1): 82-4.
8. Raederstorff D, Moser U. Borage or primrose oil added to standardized diets are equivalent sources for gamma-linolenic acid in rats. *Lipids.* 1992 Dec; 27 (12): 1018-23.
9. Bayles B, Usatine R. Evening primrose oil. *American Family Physician.* 2009; 80 (12): 1405-1408.
10. Martens-Lobenhoffer J, Meyer FP. Pharmacokinetic data of gamma-linoleic acid in healthy volunteers after the administration of evening primrose oil (Epogram). *Int J Clin Pharmacol Ther*. 1998; 36; 363-366.
11. Bamford JTM, Ray S, Musekiwa A, et al. Oral evening primrose oil and borage oil for eczema. *Cochrane Database of Systematic Reviews.* 2013; (4): CD004416. Accessed at https://www.cochranelibrary.com/tools/privacy#nccih-linking-policy on January 23, 2020.
12. Pruthi S, Wahner-Roedler DL, Torkelson CJ, et al. Vitamin E and evening primrose oil for management of cyclical mastalgia: a randomized pilot study. *Altern Med Rev*. 2010; 15 (1): 59-67.
13. McGregor L, Smith AD, Sidey M, Belin J, Zilkha KJ, McGregor JL. Effects of dietary linoleic acid and gamma linolenic acid on platelet of patients with multiple sclerosis. *Acta Neuro Scand*. 1989; 80 (1): 23-27
14. Blommers J, de Lange-de Klerk ES, Kuik DJ, et al. Evening primrose oil and fish oil for severe chronic mastalgia: a randomized, double-blind, controlled trial. *Am J Obstet Gynecol*. 2002; 187 (5): 1389-1394

15. Pruthi S, Wahner-Roedler DL, Torkelson CJ, et al. Vitamin E and evening primrose oil for management of cyclical mastalgia: a randomized pilot study. *Altern Med Rev*. 2010; 15 (1): 59-67
16. Barabino S, Rolando M, Camicione P, et al. Systemic linoleic and gamma-linolenic acid therapy in dry eye syndrome with an inflammatory component. *Cornea*. 2003; 22 (2): 97-101
17. Qureshi S, Sultan N. Topical nonsteroidal anti-inflammatory drugs versus oil of evening primrose in the treatment of mastalgia. *Surgeon*. 2005; 3(1): 7-10
18. Osman M, Badawi E. Evening primrose oil reducing serum lithium concentration. *Ther Adv Psychopharmacol*. 2016; 6 (5): 343-344
19. Hiroshi M, Zui F, Hideko A, et al. Crystal structure of an anticoagulant protein in complex with the Gla domain of factor X. *Proc Natl Acad Sci U S A.* 2001; 98 (13): 7230–7234.
20. Karl M, Björn A, Ing-Marie P, et al. Antithrombotic and anticoagulant effects of wild type and Gla-domain mutated human activated protein C in rats. *Thrombosis Research.* 2007; 120 (4): 531-539.
21. Ralf K , Thilo K, Ralf W, et al. Relation of circulating Matrix Gla-Protein and anticoagulation status in patients with aortic valve calcification. *Thromb Haemost.* 2009 Apr; 101 (4): 706-13.
22. David G, Ruth B, Thomas A, et al. A new oral anticoagulant: The 50-year challenge. *Nature Reviews Drug Discovery* 2004; 3 (8): 649-59
23. Giangrande PL. Six characters in search of an author: the history of the nomenclature of coagulation factors. *Br. J. Haematol*. 2003; **121** (5): 703–12.
24. Graham B, Andrew B, Nessar A. Blood Science - Principles and Pathology: Own work (Based on Figure 7.5 on page 167 of "Blood Science: principles and pathology", Publishers Wiley Blackwell (2014) ISBN: 978-1-118-35146-8). https://en.m.wikipedia.org/wiki/File:Coagulation_in_vivo.png.
25. Furie B, Furie BC. Thrombus formation in vivo. *J. Clin. Invest*. 2005; 115 (12): 3355–62.