

Flushing and pruritus secondary to prescription fish oil ingestion in a patient with allergy to fish

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Received: 3 April 2014 / Accepted: 16 September 2014
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Abstract *Background* A brand of fish oil capsules contains omega-3 fatty acids obtained from several fish sources. Although the manufacturer calls for caution in patients with fish hypersensitivity, insufficient data is available to make a definitive recommendation regarding its use in this population. *Case presentation* A patient with documented seafood allergy presented to the emergency department 4 days after the initiation of prescription brand name fish oil capsules complaining of chest tightness, shortness of breath, tingling of upper extremities, flushing, and pruritus that was minimally relieved by excessive nonprescription diphenhydramine administration. During subsequent follow-up, the patient reported that all symptoms had resolved within 5 days of discontinuing the medication and 3 days of disposing of her pillbox and all medications that had come in contact with the fish oil capsules. *Conclusion* Due to the patient's allergic history, timing of onset/offset of the reaction, laboratory evidence, and the use of the Naranjo probability scale, prescription fish oil capsules were deemed the probable cause of this patient's pruritus and flushing of the face and trunk. Practitioners and patients should always ensure they have an updated list of allergies

within the patient's medical record that includes medications as well as foods and food additives.

Keywords Allergic reaction · Allergy · Fish oil · Hypersensitivity · Omega-3-acid ethyl esters · Omega-3 fatty acids

Impacts of findings on practice

- Potential drug related problems due to allergies can possibly be avoided if practitioners ensure their patients' list of allergies is updated at every visit including allergies to medications, foods, and food additives.
- It is important to consider food and food additive allergies when starting a new medication.
- If patient is still having an allergic reaction after discontinuing the offending medication consider disposing of all medication that came into contact with the offending agent and ask patient to only take their remaining medications from their originally dispensed containers.
- Practitioners should make every attempt to ensure that a patients' listed allergies are documented among all practitioners involved in the patients' care.

Introduction

Fish and shellfish allergies are two of the most common food allergies among adults [1]. A national telephone survey of 5,529 households found a prevalence of 2.3 % for any seafood allergy, 2 % for shellfish, 0.4 % for fish, and 0.2 % for both shellfish and fish [2]. Despite the

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prevalence of seafood allergies and the frequent use of fish oil products for primary prevention of coronary heart disease and treatment of hypertriglyceridemia, little has been reported in the scientific literature pertaining to the incidence of adverse reactions to fish oil products in patients with seafood hypersensitivity. The specific brand of prescription fish oil capsules¹ discussed in this case contains a combination of ethyl esters of omega-3 fatty acids, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), from several fish sources. It is specifically indicated as an adjunct to diet to treat severe hypertriglyceridemia, ≥ 500 mg/dL³. The manufacturer lists known hypersensitivity (e.g. anaphylactic reaction) to the product or any of its components as a contraindication and further warns prescribers to use with caution in patients with known hypersensitivity to fish or shellfish [3]. Seafood allergy can be attributed to immunologic and non-immunologic responses related to the product itself through allergy to muscle proteins (e.g. β -parvalbumin, tropomyosin, arginine kinase, myosin light chain, and sarcoplasmic calcium binding protein) or non-seafood components of the product (e.g. preservatives, flavors, and coloring added during processing) [4]. Prescription fish oil capsules (see footnote 1) are manufactured via a multi-step purification process to remove environmental toxins, free-fatty acids, proteins, and other by-products from the derived crude fish oil. We describe a patient in the United States with a known seafood allergy that reported to the emergency department (ED) and eventually her primary care provider (PCP) complaining of flushing and severe pruritus after administration of fish oil capsules (see footnote 1) prescribed by another specialist involved in the patient's care.

Ethical approval

Authors obtained informed consent from the patient described for the writing and publication of this manuscript.

Case description

A 65 year old white female was prescribed omega-3-acid ethyl esters 2 grams twice daily by her hepatologist in response to a non-fasting lipid panel that showed a triglyceride level of 256 mg/dL (0–149 mg/dL). It is important to note that the patient's hepatologist and PCP did not

practice in the same clinic location or share a medical record, but did communicate regarding changes to therapy. The patient's past medical history was significant for nonalcoholic steatohepatitis with cirrhosis, type 2 diabetes, asthma, hypertension, hyperlipidemia, osteoarthritis, restless leg syndrome, migraines, anxiety and depression. Allergies recorded in PCP's record prior to prescription fish oil administration included "sulfas", penicillin, codeine oxycodone/acetaminophen, tramadol/acetaminophen, propoxyphene/acetaminophen, celecoxib, adhesive, shellfish and tuna. Her hepatologist did not have a complete allergy list in the patient's medical record. The following allergies were missing: celecoxib, adhesive, shellfish, and tuna. The patient reported taking the following medications in addition to prescription fish oil: rizatriptan, albuterol, ramipril, furosemide, carvedilol, clonazepam, spironolactone, raloxifene, lispro/lispro protamine, sitagliptan/metformin, lactulose, pregabalin, sertraline, montelukast, topiramate, simvastatin/ezetimibe, rifaximin, bifantis probiotic (Align), calcium citrate with vitamin D, magnesium, cetirizine, and niacin (Enduracin). The patient had not had any recent medication changes, with the exception of a change in formulation of OTC niacin from an extended release wax matrix product, Enduracin 500 mg every other day, to immediate release niacin 250 mg daily about 1 week prior to the addition of the prescription fish oil product. The patient reported never using ibuprofen or aspirin as prophylaxis for flushing prior to a niacin dose with either formulation. She had also been taking niacin for years without any prior complaints.

Four days after the patient started taking prescription fish oil, she went to the ED after experiencing chest tightness, shortness of breath, tingling of upper extremities, pruritus, abdominal pain, and nausea. The patient also reported facial flushing during the episode of chest tightness. Allergies listed in the ED medical record included all those previously mentioned in the PCP and hepatologist medical record in addition to olives and shellfish. Prior to her ED admission, the patient reported taking 4–6 capsules of nonprescription diphenhydramine 25 mg as a one time dose and then continued to take 25 mg one to two tablets every 2 h thereafter, which resulted in only partial relief of her pruritus. She reported never having any wheezing or bronchospasm requiring albuterol. In regard to the potential allergic reaction, eosinophils remained within normal limits at 1 % (0–7 %); however, immunoglobulin E (IgE) was not obtained during her ED visit. After myocardial infarction had been ruled out, the patient was discharged with instructions to follow up with her PCP. No discussion of a possible allergic reaction or adverse reaction to prescription fish oil occurred during her ED admission.

Upon follow up with her PCP 9 days after starting prescription fish oil capsules (5 days after ED admission),

¹ Lovaza[®] produced by Pronova Biopharma and marketed and distributed by GlaxoSmithKline in the United States of America. Pronova Biopharma also supplies same the medication under the brand name Omacor[®] in Europe using different network of partners for distribution and marketing, Takeda Pharmaceutical (Japan), Prospa (Italy), and Solvay (United Kingdom and Germany).

Table 1 The Naranjo adverse drug reaction probability scale

	Yes	No	Do not know	Score
Are there previous <i>conclusive</i> reports on this reaction?	+1	0	0	1
Did the adverse event occur after the suspected drug was administered?	+2	-1	0	2
Did the adverse reaction improve when the drug was discontinued or a <i>specific</i> antagonist was administered?	+1	0	0	1
Did the adverse reaction reappear when the drug was readministered?	+2	-1	0	0
Are there alternative causes (other than the drug) that could have on their own caused the reaction?	-1	+2	0	2
Did the reaction reappear when a placebo was given?	-1	+1	0	0
Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0
Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0
Did the patient have a similar reaction to the same or similar drugs in <i>any</i> previous exposure?	+1	0	0	0
Was the adverse event confirmed by any objective evidence?	+1	0	0	1
Total ^a				7

^a The adverse drug reaction is assigned to a probability category from the total score as follows: *definite* if the overall score is 9 or greater, *probable* for a score of 5–8, *possible* for 1–4 and *doubtful* if the score is 0

the patient reported that she had stopped taking the prescription fish oil on her own and had removed it from her pill box 2 days prior. She had significantly decreased the use of diphenhydramine since discontinuing prescription fish oil capsules but was still experiencing flushing on her face and trunk as well as significant pruritus that was not relieved by taking diphenhydramine 25 mg that morning. The patient was referred by her PCP to the clinical pharmacist for evaluation of a potential adverse drug reaction consisting of flushing on her trunk and face and severe pruritus, which was minimally relieved by excessive non-prescription diphenhydramine administration. The primary reason for referral was to determine whether the reaction was likely in response to the change in niacin formulation or the addition of the prescription fish oil product. During her interview with the clinical pharmacist, she reported having a shellfish allergy that progressively worsened from pruritis to hives to shortness of breath over the past several years and developed to further included tuna, olives and sulfites. Flushing was not observed during the visit; however, the patient was noticeably scratching throughout her interview with the clinical pharmacist and physician. In addition, she was drinking a large glass of water that she brought with her to the office visit and reported being very thirsty. The only medication the patient had taken the morning of her appointment with her PCP was spironolactone, which was in the same compartment of her pill box that previously held the prescription fish oil. At this visit, a serum IgE concentration was drawn which was elevated at 132 IU/mL (0–100 IU/mL), although eosinophils remained within normal limits at 2 % (0–7 %). All allergies were updated in the medical record and the patient was instructed to dispose of all medications that had come in contact with the prescription fish oil product, dispose of or clean out the pill box and start taking medications directly

from the bottles from which the medications were originally dispensed.

During a phone follow up 1 week after her PCP appointment, the patient reported that all symptoms had resolved within 3 days and that she was no longer requiring diphenhydramine. She continued to take the niacin throughout this 2-week time period. In addition, an epinephrine pen autoinjector was prescribed for the patient to prevent future anaphylaxis associated with her fish allergy. A follow up lab appointment 3 weeks later showed a decrease in IgE to 117 IU/ml and a fasting triglyceride level of 143 mg/dL. These lab results were relayed to the hepatologist's office along with additional missing allergies to be added to the patient's profile. The patient's PCP noted the reaction and decided not to rechallenge with a brand of fish oil capsules since it was not indicated, with adequately controlled triglycerides.

Discussion

We performed a PubMed search (through August 2013) using the terms “fish oil”, “omega-3 fatty acids”, “omega-3-acid ethyl esters” or “Lovaza[®]” and “adverse reaction”, “hypersensitivity”, or “allergy” in various combinations to identify previous reports of adverse reactions to any fish oil products in patients allergic to fish or shellfish. The only relevant publication was a case report of a patient who experienced recurrent anaphylaxis after ingestion of a single fish oil capsule [5].

The timing of the onset of the adverse reaction makes the change in niacin formulation an unlikely cause. The patient discontinued an extended release wax matrix niacin product 1 week prior to starting the fish oil and began taking immediate release niacin one and a half weeks

before presenting to the ED. This raised concern because immediate release niacin has been associated with more flushing than extended release niacin [6]. However, the patient continued to take the immediate release niacin throughout the 2-week evaluation process and after the symptoms resolved.

This adverse reaction can more likely be attributed to the prescription fish oil product due to the patient's known hypersensitivity to seafood and the onset of the reaction aligning more closely with the initiation of the fish oil 4 days prior to presenting to the ED. Persistence of symptoms after discontinuation of the omega-3-acid ethyl esters can be explained by the continuation of medications that had been in direct contact with the fish oil capsules in the patient's pill box. The symptoms resolved within 3 days once the patient began taking medications directly from their originally dispensed containers. This adverse reaction was confirmed by the elevation in the patient's IgE level after ingestion followed by a subsequent decline in IgE after discontinuation of the fish oil product. Given the above information, the Naranjo probability scale was performed by the PCP and clinical pharmacist involved in her care, which classified the adverse drug reaction as having a probable association with omega-3-acid ethyl esters (Table 1) [7].

Conclusion

Practitioners should exercise caution and monitor patients for adverse reactions when initiating fish oil products in

those with fish or shellfish allergies. To avoid adverse drug events, practitioners and patients should always ensure that an up to date list of allergies is recorded in the medical record, which includes medications as well as foods and food additives.

Funding There is no funding for the writing or publishing of this manuscript.

Conflicts of interest The authors have no conflicts of interest to disclose.

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