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Potential Benefits of Icosapent Ethyl on the Lipid Profile: Case Studies

Daniel E. Hilleman and Mark A. Malesker

Department of Pharmacy Practice, Creighton University School of Pharmacy and Health Professions, Omaha, NE, USA.

ABSTRACT: The cardiovascular benefits of marine-derived omega-3 fatty acids are supported by epidemiologic and clinical studies. Both healthy patients and those with confirmed coronary heart disease are advised by the American Heart Association to consume omega-3 fatty acids either through dietary fatty fish or fish oil products. We present two case reports of patients with dyslipidemia who were switched from an omega-3 dietary supplement or a prescription omega-3 drug containing eicosapentaenoic acid (EPA) plus docosahexaenoic acid (DHA) to a new prescription EPA-only drug, icosapent ethyl (IPE). Products containing a combination of EPA and DHA, including dietary supplements and prescription products, are more likely to increase low-density lipoprotein cholesterol (LDL-C) levels compared with pure EPA-only products. The lipid profiles of these two patients were improved with IPE treatment, illustrating the potentially favorable effects of IPE compared with other products containing both EPA and DHA.

KEYWORDS: omega-3 fatty acids, fish oil, eicosapentaenoic acid, docosahexaenoic acid, lipids, icosapent ethyl

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CORRESPONDENCE: hilleman@creighton.edu

Introduction

Epidemiologic and clinical studies support the cardiovascular benefits of marine-derived omega-3 fatty acids (OM-3 FA).[1–5] Potential mechanisms for the cardioprotective effects of OM-3 FA include reducing triglyceride (TG) levels, stabilizing atherosclerotic plaque, exerting antiarrhythmic, antithrombotic, and anti-inflammatory effects, lowering blood pressure, and improving endothelial function.[4] The American Heart Association (AHA) recommends that all adults eat fatty fish at least twice a week, and that adults with documented coronary heart disease (CHD) ingest approximately 1 gram of OM-3 FA (eicosapentaenoic acid [EPA] plus docosahexaenoic acid [DHA]) per day.[6] Increasing OM-3 FA consumption through food sources is preferable; however, these patients may not be able to get enough OM-3 FA through diet alone.[7] As a result, the AHA recommends that OM-3 FA supplementation may be taken in the form of fish oil capsules.[7]

There are currently two FDA-approved OM-3 FA products available by prescription. Each 1-gram capsule of omega-3 acid ethyl esters (OM3EE; Lovaza®; GlaxoSmithKline, Research Triangle Park, NC, USA) contains at least 900 mg of the ethyl esters of OM-3 FA, which includes approximately 465 mg of EPA and 375 mg of DHA.[8] Icosapent ethyl (IPE; Vascepa®; Amarin Pharma Inc., Bedminster, NJ, USA) is an ethyl ester of EPA with each capsule containing 1 gram of IPE.[9] Both products are only approved as adjuncts to diet to reduce TG levels in adults with severe (≥500 mg/dL) hypertriglyceridemia.[8,9] Products containing a combination of EPA and DHA, including dietary supplements and prescription products, are more likely to increase low-density lipoprotein cholesterol (LDL-C) levels compared with pure EPA-only products, especially in patients not receiving statin therapy.[10–14]

We report two cases of patients who were switched from a dietary supplement or a prescription medication to IPE. The results observed in these patients may be illustrative of the favorable effects of this new OM-3 FA product.

Case Report 1

A man in his late 50s with a history of hypertension, dyslipidemia, osteoarthritis, and type 2 diabetes mellitus was

taking telmisartan 80 mg/d, amlodipine 10 mg/d, atorvastatin 40 mg/d, metformin 500 mg twice daily, and Carlson EPA Gems® (Carlson Nutritional Supplements, Arlington Heights, IL, USA), 2 capsules twice daily with meals. He had been taking all of his prescription medications for a minimum of 4 years, with good compliance based on prescription refill records. His blood pressure (128/82 mm Hg) and hemoglobin A_{1c} (A_{1c}) (7.1%) were reasonably well controlled based on his most recent laboratory results. His lipid profile is summarized in Table 1. After 8 weeks of treatment with Carlson EPA Gems, a repeat lipid profile was obtained. After reviewing his lipid profile, the patient's physician prescribed IPE 2 capsules twice daily with meals. The results of his lipid profile after 6 weeks of IPE therapy are shown in Table 1. He had not experienced any adverse effects with Carlson EPA Gems, and did not report any adverse effects with IPE. There was substantial improvement in the patient's lipid profile with IPE treatment compared with the use of the Carlson EPA Gems specific to total cholesterol, LDL-C, TG, and non-high-density lipoprotein cholesterol (non-HDL-C) levels. Both OM-3 FA products produced generally similar results regarding HDL-C levels compared with pretreatment levels.

Case Report 2

The patient, a woman in her early 60s with a history of hypertension, type 2 diabetes mellitus, and dyslipidemia, was taking hydrochlorothiazide 25 mg/d, ramipril 10 mg/d, metoprolol-XL 50 mg/d, metformin 1 g twice daily, saxagliptin 5 mg/d, and prescription OM3EE 2 g twice daily. The patient did not tolerate any statin regimen due to muscle complaints. She had been taking this medical regimen for at least 2 years, with good compliance based on prescription refill records. Her most recent blood pressure (136/88 mmHg) and A_{1c} laboratory results (6.8%) indicated reasonable control of her hypertension and diabetes. Her lipid profile prior to and after OM3EE therapy are summarized in Table 1. At her most recent physician's visit (at which time a repeat lipid profile was obtained), the patient's physician discontinued her OM3EE and prescribed IPE 2 capsules twice daily. The results of the patient's lipid profile after 6 weeks of IPE therapy are shown in Table 1. She had reported no adverse effects with OM3EE therapy, and did not report any adverse effects with IPE therapy. There was substantial improvement in the patient's lipid profile with IPE compared with OM3EE specific to total cholesterol, LDL-C, and non-HDL-C levels. Both OM-3 FA products produced generally similar results with TG and HDL-C levels compared with pretreatment levels.

Table 1. Case presentations: Lipid profile results prior to and after the use of each OM-3 FA product.

CASE REPORT 1			
PARAMETER	**PRETREATMENT (mg/dL)**	**EPA GEMS (mg/dL)**	**IPE (mg/dL)**
Total cholesterol	153	204	148
LDL-C	45	100	47
HDL-C	36	43	44
Triglycerides	361	304	198
Non-HDL-C	117	161	104
CASE REPORT 2			
PARAMETER	**PRETREATMENT (mg/dL)**	**OM3EE (mg/dL)**	**IPE (mg/dL)**
Total cholesterol	230	260	234
LDL-C	140	185	148
HDL-C	50	53	54
Triglycerides	348	301	285
Non-HDL-C	180	207	180

Abbreviations: HDL-C, high-density lipoprotein cholesterol; IPE, icosapent ethyl; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol (total cholesterol – HDL-C = non-HDL-C); OM3EE, omega-3 acid ethyl esters; OM-3 FA, omega-3 fatty acid.

Discussion

These two cases illustrate the potential advantage of a pure ethyl ester of EPA (IPE) compared with other OM-3 FA products containing combinations of EPA and DHA. The combination products are more likely to result in increases in LDL-C levels, especially in patients not taking a statin.[10–13] Although technically, neither patient met the criteria for the FDA-approved indication for prescription OM-3 FA products,[8,9] these agents are often prescribed for patients with TG levels in the 250 to 500 mg/dL range. In addition, the AHA recommends lower doses (approximately 1 g/day) of OM-3 FA products for patients who cannot or will not eat fatty fish on a regular basis.[7] Although a recently updated position statement from The American Diabetes Association does not recommend omega-3 supplements for people with diabetes for the prevention or treatment of cardiovascular events, these guidelines were not available at the time of treatment for the 2 patients reported here; the updated guidelines do, however, support a TG goal of <150 mg/dL, a level well below that encountered with the 2 patients reported here.[15] The Reduction in Cardiovascular Events with EPA-Intervention Trial (REDUCE-IT; NCT01492361) is underway to investigate the efficacy of IPE in preventing cardiovascular events in high-risk, statin-treated patients with hypertriglyceridemia.[16]

In the first case presentation, the patient was taking a statin with a very low LDL-C level prior to starting Carlson EPA Gems, a dietary supplement form of OM-3 FA.[17] It is believed that the patient initiated this therapy on his own without advice from his physician. The product information indicates that each Carlson EPA Gem 1-g capsule contains 580 mg of OM-3 FA from fish oil, 400 mg of EPA, 100 mg of DHA, 10 IU of vitamin E, and 80 mg of OM-3 FA from other sources. Although it cannot be determined based on the label, the actual amount of OM-3 FA in the Carlson product is impossible to determine. One might conclude that the 580 mg of OM-3 FA in the Carlson product is based on the inclusion of 400 mg of EPA, 100 mg of DHA, and 80 mg of OM-3 FA from other

sources. But the 80 mg is not from fish oil, so only 500 mg would be OM-3 FA from fish oil and not 580 mg as stated on the label. It is also unlikely that the 1-g capsule would contain 580 mg OM-3 FA plus 400 mg EPA plus 100 mg DHA plus 80 mg of OM-3 FA for a total of 1160 mg of OM-3 FA. This lack of active ingredient clarity is just one of the disadvantages of using a dietary supplement form of OM-3 FA. In any event, substantial increases in total cholesterol, LDL-C, and non-HDL-C levels were observed with Carlson EPA Gems but not with IPE. In addition, TG level reductions were substantially greater with IPE than with the dietary supplement product.

In the second case presentation, the patient was not taking a statin. The result of OM-3 FA therapy in this patient, who used the two available prescription products, is consistent with the prescribing information for each.[8,9] In patients not taking a statin, OM3EE can be associated with increases in LDL-C levels, while IPE does not affect LDL-C levels in such patients. In this specific case, OM3EE was associated with substantial increases in LDL-C, total cholesterol, and non-HDL-C levels, while no substantial increases were observed in these lipids with IPE. The effects of the two agents on TG and HDL-C levels were generally similar.

The use of OM-3 FA products sold as dietary supplements without prescription have a number of limitations including clarity of labeling regarding active ingredients, questionable purity, and a lack of clinical trial evidence of efficacy and safety.[18–20] Given that the two FDA-approved OM-3 FA products are priced similarly[21,22] and have identical indications,[8,9] it would appear that IPE may have a preferable impact on patient lipid profiles compared with OM3EE, perhaps more so in patients not taking statins. Although this report is limited by 2 individual cases, from a drug product selection and formulary inclusion perspective, IPE may be a preferred option for prescription OM-3 FA products. Further investigation and/or observational studies involving greater patient numbers, longer study duration, and between-patient statistical analyses are needed to help clarify the potential lipid effects of switching between OM-3 products.

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Author Contributions

Wrote the first draft of the manuscript: DEH, MAM. Agree with manuscript results and conclusions: DEH, MAM. Jointly developed the structure and arguments for the paper: DEH, MAM. Made critical revisions and approved final version: DEH, MAM. All authors reviewed and approved of the final manuscript.

DISCLOSURES AND ETHICS

As a requirement of publication the authors have provided signed confirmation of their compliance with ethical and legal obligations including but not limited to compliance with ICMJE authorship and competing interests guidelines, that the article is neither under consideration for publication nor published elsewhere, of their compliance with legal and ethical guidelines concerning human and animal research participants (if applicable), and that permission has been obtained for reproduction of any copyrighted material. This article was subject to blind, independent, expert peer review. The reviewers reported no competing interests.

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