Expert Opinion on Pharmacotherapy

ISSN: 1465-6566 (Print) 1744-7666 (Online) Journal homepage: informahealthcare.com/journals/ieop20

Do we need 'new' omega-3 polyunsaturated fatty acids formulations?

Arrigo FG Cicero, Martino Morbini & Claudio Borghi

To cite this article: Arrigo FG Cicero, Martino Morbini & Claudio Borghi (2015) Do we need 'new' omega-3 polyunsaturated fatty acids formulations?, Expert Opinion on Pharmacotherapy, 16:3, 285-288, DOI: 10.1517/14656566.2015.991308

To link to this article: https://doi.org/10.1517/14656566.2015.991308

Published online: 04 Dec 2014.

EXPERT OPINION

Do we need 'new' omega-3 polyunsaturated fatty acids formulations?

Arrigo FG Cicero[†], Martino Morbini & Claudio Borghi
[†]*Hypertension Research Center, Bologna, Italy*

The therapeutic value of omega-3 polyunsaturated fatty acids (PUFAs), mainly (but not only) found in fish oils, eicosapentaenoic and docosahexaenoic acids (EPA and DHA, respectively), has been extensively studied in a wide variety of disease conditions, predominantly in cardiovascular disease. However, the significant difference in efficacy observed in various conditions with different dosages seems to be at least partly related to the large discrepancy in quality of the product and to the bioavailability of the omega-3 PUFA. The research of new sources (e.g., from arctic Krill oil) and pharmaceutical forms of omega-3 PUFA (e.g., omega-3 carboxylic acids) is needed in order to detect the one with the best bioavailability and efficacy, and with a parallel reduction in the production costs. There is also the need to understand if long-term PUFA supplementation could increase the efficacy of the already-available evidence–based therapies for cardiovascular disease prevention and for the management of the diseases where the use of PUFA could have a possible improving effect.

Keywords: bioavailability, docosahexaenoic acid, eicosapentaenoic acid, fish oil, polyunsaturated fatty acid

Expert Opin. Pharmacother. (2015) ***16****(3):285-288*

The therapeutic value of omega-3 polyunsaturated fatty acids (PUFAs), mainly (but not only) found in fish oils, eicosapentaenoic and docosahexaenoic acids (EPA and DHA, respectively), has been extensively studied in a wide variety of disease conditions, predominantly in cardiovascular disease. In fact, PUFAs have a large number of pharmacological properties that justify their dietary supplementation in a considerable number of human diseases: metabolic (e.g., hypertriglyceridemia, non-alcoholic steatohepatitis, polycystic ovary syndrome), inflammatory (e.g., allergy, chronic inflammatory bowel diseases), ocular (e.g., age-related degenerative macular disease), degenerative (osteoarthrosis) and psychiatric (e.g., psychosis) diseases (**Table 1**) [1].

The significant difference in efficacy observed in various conditions depends, of course, on the large variability in baseline omega-3 PUFA plasma concentration in study participants (often even not tested), the use of inappropriate dosage and possible wrong ratio between EPA and DHA. Moreover, the omega-3 free fatty acid form probably does not provide much of an advantage against a high fat dietary background but may be advantageous against a low fat background or when taken without a meal. On the other side, that difference in efficacy with different dosages seems to be at least partly related to the large discrepancy in quality of the product and to the bioavailability of the omega-3 PUFA. In particular, the contrasting results observed with supplementation of omega-3 PUFA in cardiovascular disease prevention or treatment have been attributed to the fact that the serum level of omega-3 PUFA is more strongly linked to the clinical outcome than to the omega-3 PUFA dose assumed [1].

Thus, on the one hand, the epidemiology clearly supports the hypothesis that omega-3 PUFA consumption is associated with a lower risk of cardiovascular

informa
healthcare

10.1517/14656566.2015.991308 © 2015 Informa UK, Ltd. ISSN 1465-6566, e-ISSN 1744-7666

Table 1. Suggested indication for omega-3 polyunsaturated fatty acids supplementation in clinical practice based on RCTs and meta-analyses.

Field	Disease	Level of evidence
Cardiovascular	Hypertriglyceridemia	Meta-analysis of RCTs
	Post-infarction arrhythmia	Meta-analysis of RCTs
	Hypertension	Meta-analysis of RCTs
Pneumology	Asthma prevention	Meta-analysis of epidemiological data
	Chronic respiratory diseases	RCTs
	Cystic fibrosis	RCTs
Autoimmune disease	Allergy/atopic eczema	RCTs
	Rheumatoid arthritis	RCTs
	Psoriasis	RCTs
	Inflammatory bowel diseases	RCTs
Ophthalmology	Age-related degenerative macular disease	RCTs
	Dry eyes	RCTs
Psychiatry	Psychosis	RCTs
	Depression	Meta-analysis of RCTs
Neurology	Relapsing-remitting multiple sclerosis	RCTs
	Some epilepsies	RCTs
Nephrology	IgA nephropathy	RCTs
Dermatology	Cutaneous wounds	RCTs

Data taken from [1].
RCT: Randomized clinical trial.

disease, in regard to atherosclerosis and arrhythmias. However, epidemiological studies cannot determine the cause and effect because of the likely confounding factors (e.g., high risk subjects could be more likely to take fish oil supplements than subjects with a lower cardiovascular risk). Moreover, the effects of fish consumption in observational studies could be related to a combined effect of omega-3 PUFA and other micronutrients (e.g., zinc or vitamin D) that cannot be observed with the supplementation of omega-3 PUFA alone. In fact, recent meta-analyses of randomized clinical trials, including various kinds of patients and various dosages and pharmaceutical formulations of omega-3 PUFA, seem to reduce the emphasis on presumed omega-3 PUFA protective effects [2], probably because of a low absolute risk as a consequence of the state-of-the-art drug treatment. When evaluating only patients in secondary prevention, the protective effect seems to be however preserved [3].

The cardiovascular protective effect associated with omega-3 PUFA supplementation seems to be also connected with their multiple pharmacological effects (**Table 2**), such as the antiplatelet action (more evident in patients in secondary prevention), decreasing thrombin formation and oxidative stress and favorably altering fibrin clot properties [4]. Moreover, adding omega-3 PUFA to low-dosed aspirin reduces aspirin resistance, with an effect similar to the increase of aspirin dose [5]: this could have some positive effects in terms of gastrointestinal tolerability of aspirin, beyond all the otherwise known omega-3 PUFA actions. Omega-3 PUFAs could have mild but significant antihypertensive effects, mediated by their ability to improve the prostanoid metabolism, to contrast the formation of thromboxane A_2, a potent vasoconstrictor, and to enhance that of prostaglandin I_3 (PGI_3), a well-known vasodilator. Moreover, EPA lowers the tissue levels of arachidonic acid and enhances that of γ-linolenic acid, the precursor of PGE_1, another vasodilator agent. Therefore, omega-3 PUFA also suppresses ACE activity, reduces angiotensin II formation, enhances endothelial nitric oxide generation and suppresses TGF-β expression. Besides NO, eicosanoids and renin related effects, omega-3 PUFA may affect intracellular calcium balance of vascular smooth muscle cells by interaction with K +ATP and Ca^{2+} channels and may have a role in their proliferation, migration and apoptosis by multiple mechanisms [6].

What about the long-term omega-3 PUFA safety? In epidemiological studies, the intake of PUFA seems to be mildly related to the incidence of type 2 diabetes [7], although this effect was never clearly demonstrated in long-term intervention trials. Concerns have also been raised regarding adverse effects on low-density lipoprotein (LDL) cholesterol plasma level and oxidative stress, but increases in LDL cholesterol are modest and studies into oxidative stress have been contradictory. Overall, these effects are unlikely to be dominant, given the apparent cardiac benefits of omega-3 PUFA [8]. Moreover, the mild prooxidant effect of PUFA could be balanced by adding, to the formulation, an adequate dosage of antioxidants, such as vitamin E. Therefore, omega-3 PUFA may exert a dose-related effect on bleeding time, but an objective assessment of the evidence for clinically significant bleeding reveals that such concerns are unfounded [9]. More specific concerns regarding dietary fish relate to environmental contaminants, and mercury in fish may attenuate their cardioprotective effects [10]. However, a risk–benefit analysis of changes in population fish consumption concluded that the net public health impact of a reduced fish intake because of poisoning fear is negative [11]. Moreover, contaminants accumulate in larger, predatory fish;

Table 2. Pharmacological effects of omega-3 polyunsaturated fatty acids demonstrated in humans with potential relevance in cardiovascular disease prevention.

Interaction with omega-6 fatty acids
—Production of inactive leukotrienes and thromboxanes
Decrease in biological mediators
—IL-1, IL-2, TNF, PDGF
Effect on blood lipoprotein levels
—Decrease in plasma VLDL and triglyceride levels
Hypotensive effect
—Changes in eicosanoids, in blood viscosity, in hormonal-cellular response, in renin secretion, decreased response to vasopressors
Decrease in plasma viscosity
—Decreased plasma fibrinogen
Effects on coagulation
—Prolonged bleeding time, decrease in fibrinogen, factor VII, von Willebrand factor, increase in fibrinolysis
Increased arterial compliance
—Increased production of nitric oxide
Effects on adhesion molecules
—Decreased ICAM-1, VCAM-1, E-selectin levels
Effects on vascular smooth muscle cells
—Modulation of proliferation, migration and apoptosis and improved vasoreactivity by interaction with intracellular calcium dynamics

ICAM-1: Intercellular adhesion molecule 1; PDGF: Platelet-derived growth factor; VCAM-1: Vascular cell adhesion molecule 1; VLDL: Very-low-density lipoprotein.

therefore, the consumption of a variety of fish (or of fish oil supplements) should minimize any possible adverse effects. On the other side, consumption of equal amounts of EPA and DHA from oily fish weekly, or in the form of capsules daily, are nearly equally effective [12]; nonetheless, capsules are usually safer in regard to eventual contaminant contents as they are not a source of other fatty acids and of energy. Finally, no significant negative interaction has been observed until now between most of the drugs and omega-3 PUFAs [13], with the only exemption of the above-stated small increasing effect of anticoagulant drugs for the use of large doses [9].

In this issue of *Expert Opinion in Pharmacotherapy*, an interesting review discusses the efficacy and safety data relating to the clinical use of omega-3 PUFA carboxylic acids (also called omega-3 free fatty acid), with higher bioavailability than other pharmaceutical forms of omega-3 PUFA, potentially resulting in efficacy at lower doses and less dependence on meal relationship [14]. In fact, omega-3 carboxylic acids are directly absorbed in the small intestine and quickly re-esterified into triglycerides, which then enter the lymphatic system and the thoracic duct and flow to the superior vena cava. Their C_{max} (maximum EPA and DHA plasma concentrations) is reached within 5 – 9 h after administration and steady-state concentrations of EPA and DHA are achieved within 2 weeks of repeat daily dosing. Following repeated dosing, their half-life is 37 h for EPA and 46 h for DHA. The lower dose will be associated to an improved compliance and less intensive and frequent fish aftertaste, witnessed in all Phase II, Phase III and post-marketing trials [15]. A large long-term trial with hard outcomes (morbidity and mortality) has also been planned in order to confirm the efficacy and safety of the newly proposed omega-3 PUFA formulation — "Outcomes Study to Assess Statin Residual Risk Reduction with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia". This trial will enroll around 30,000 subjects at high risk of developing cardiovascular disease, with residual atherogenic dyslipidemia despite optimal LDL cholesterol control (< 100 mg/dL) by statin +/- ezetimibe treatment, who will be randomized to a treatment with 4 g/day omega-3 PUFA carboxylic acids or placebo (corn oil). Results are expected in 2019 or when around 1600 primary events (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, emergent/elective coronary revascularization or hospitalization for unstable angina) will be registered.

Expert opinion

The priority of cardiovascular disease prevention is to reach an optimal control of plasma LDL-cholesterol level; however, a part of the residual cardiovascular risk observed in large clinical trials seems to be related to the parallel presence of suboptimal triglycerides level, *per se* associated with a lower level of circulating high-density lipoprotein cholesterol. At the moment, the most valuable treatment is fenofibrate, the efficacy or tolerability of other pharmacological treatments being under discussion. In the context of a progressively aging and medicalized population, the availability of safe drugs, the metabolism of which is not affected by liver or kidney function, with a nearly not existing risk of pharmacological interactions and potentially affecting more diseases at the same time, is of particular interest. The research of new sources (e.g., from arctic Krill oil) and pharmaceutical forms of omega-3 PUFA (e.g., omega-3 PUFA carboxylic acids) is needed in order to detect the one with the best bioavailability and efficacy, and with a parallel reduction in the production costs to face the progressive fish stocks dwindling. For new sources of omega-3 PUFA we also need to look at the DHA:EPA ratio and whether this is right for clinical efficacy

for various conditions, apparently because EPA is more effective for cognitive/psychological effects, whereas DHA + EPA are more effective for cardiovascular effects.

There is also the need to understand if long-term omega-3 PUFA supplementation could increase the efficacy of the already-available gold standard for cardiovascular disease prevention and for the management of the diseases where the use of omega-3 PUFA could have a possible improving effect.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents, received or pending, or royalties.

Bibliography

1. Cicero AF, Reggi A, Parini A, et al. Application of polyunsaturated fatty acids in internal medicine: beyond the established cardiovascular effects. Arch Med Sci 2012;8(5):784-93
2. Rizos EC, Ntzani EE, Bika E, et al. Association between omega-3 fatty acid supplementation and risk of major cardiovascular disease events: a systematic review and meta-analysis. JAMA 2012;308(10):1024-33
3. Casula M, Soranna D, Catapano AL, et al. Long-term effect of high dose omega-3 fatty acid supplementation for secondary prevention of cardiovascular outcomes: a meta-analysis of randomized, placebo controlled trials. Atheroscler Suppl 2013;14(2):243-51
4. Gao LG, Cao J, Mao QX, et al. Influence of omega-3 polyunsaturated fatty acid-supplementation on platelet aggregation in humans: a meta-analysis of randomized controlled trials. Atherosclerosis 2013;226(2):328-34
5. Lev EI, Solodky A, Harel N, et al. Treatment of aspirin-resistant patients with omega-3 fatty acids versus aspirin dose escalation. J Am Coll Cardiol 2010;55(2):114-21
6. Cicero AF, Ertek S, Borghi C. Omega-3 polyunsaturated fatty acids: their potential role in blood pressure prevention and management. Curr Vasc Pharmacol 2009;7(3):330-7
7. Zhou Y, Tian C, Jia C. Association of fish and n-3 fatty acid intake with the risk of type 2 diabetes: a meta-analysis of prospective studies. Br J Nutr 2012;108(3):408-17
8. Hooper L, Thompson RL, Harrison RA, et al. Risks and benefits of omega 3 fats for mortality, cardiovascular disease, and cancer: systematic review. Brit Med J 2006;332:752-60
9. Harris WS. Expert opinion: omega-3 fatty acids and bleeding-cause for concern? Am J Cardiol 2007;99(6A):44C-6C
10. Guallar E, Sanz-Gallardo MI, van't Veer P, et al. Mercury, fish oils, and the risk of myocardial infarction. Heavy Metals and Myocardial Infarction Study Group. N Engl J Med 2002;347(22):1747-54
11. Cohen JT, Bellinger DC, Connor WE, et al. A quantitative risk-benefit analysis of changes in population fish consumption. Am J Prev Med 2005;29(4):325-34
12. Harris WS, Pottala JV, Sands SA, et al. Comparison of the effects of fish and fish oil capsules on the n-3 fatty acid content of blood cells and plasma phospholipids. Am J Clin Nutr 2007;86(6):1621-5
13. Di Minno MN, Tremoli E, Tufano A, et al. Exploring newer cardioprotective strategies: ω-3 fatty acids in perspective. Thromb Haemost 2010;104(4):664-80
14. Roth EM. Eicosapentaenoic acid + docosahexaenoic acid for the treatment of severe hypertriglyceridemia. Exp Opin Pharmacother 2014. [Epub ahead of print]
15. Blair HA, Dhillon S. Omega-3 carboxylic acids (Epanova): a review of its use in patients with severe hypertriglyceridemia. Am J Cardiovasc Drugs 2014;14(5):393-400

Affiliation

Arrigo FG Cicero[†1,2] MD PhD, Martino Morbini[1] MD & Claudio Borghi[1] MD
[†]Author for correspondence
[1]Alma Mater Studiorum University of Bologna, Medical and Surgical Sciences Department, Bologna, Italy
[2]Hypertension Research Center, Poliambulatorio Pad. 2, Via Albertoni, 15, 40138 Bologna, Italy,
Tel: +39 516362224
Fax: +39 516826125
E-mail: afgcicero@cardionet.it