Icosapent ethyl

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Introduction

The consumption of fish oil has been associated with reduced cardiovascular risk in Greenland Eskimos, who traditionally follow a pescatarian diet. The regular intake of n-3 (also called omega-3) fatty acids, which are present in fish oil, has been suggested as being of potential benefit in the primary and secondary prevention of coronary heart disease, but meta-analysis of trials of n-3 fatty acids have demonstrated no significant reduction in major cardiovascular events. Icosapent ethyl is a fish oil derivative which has been demonstrated to reduce triglyceride levels without increasing low density lipid (LDL) cholesterol.

Pharmacology

Isocapent ethyl is a semi-synthetic, long-chain fatty acid ethyl ester condensed from the carboxy group of icosapentaenoic acid and an ethanol hydroxyl group. Following administration, isocapent ethyl is de-esterified and converted into active eicosapentaenoic acid (EPA) which is absorbed in the small bowel. Peak plasma concentration is achieved approximately five hours following oral ingestion. It is almost completely incorporated into phospholipids, triglycerides and cholesteryl esters, with less than one percent remaining in circulating plasma. It is hepatically metabolised into acetyl coenzyme A by beta-oxidation with a biological half-life of 89 hours and plasma clearance rate of 684 ml/hr.

EPA is a naturally existing long-chain fatty acid found in oily fish and seafood, and there is no evidence of toxicity from high dose regimens from existing literature. EPA is hypothesised to reduce triglyceride level through the reduction of hepatic very-low-density lipoprotein (VLDL) triglyceride synthesis/secretion and through enhanced clearance of triglycerides from VLDLs in the circulation. The mechanism of action is uncertain but is believed to involve acyl-CoA:1,2-diacylglycerol acyltransferase inhibition, decreased hepatic lipogenesis or increased beta-oxidation and plasma lipoprotein lipase activity (**Figure 1**).

Trials of safety and efficacy

The MARINE trial compared icosapent ethyl 2g or 4g/day versus placebo in 229 patients with elevated triglyceride levels with or without background statin therapy (1). Other triglyceride-lowering therapies such as fibrates, and fish oils containing both eicosapentaenoic acid and docosahexaenoic acid, can substantially increase LDL cholesterol levels when administered to patients with very high TG levels. In MARINE icosapent ethyl significantly decreased triglyceride levels at 12 weeks with no change in the placebo-corrected LDL cholesterol levels. The most common adverse event was gastrointestinal upset.

The ANCHOR study compared icosapent ethyl 2g/day or 4g/day versus placebo in 702 statin-treated patients who were at high risk of coronary disease with residual elevation of triglycerides despite controlled LDL cholesterol levels (2). A 12 weeks weeks it demonstrated a decrease in placebo-adjusted triglyceride levels from baseline by 10% and 21% in the 2g/day and 4g/day arms respectively. LDL cholesterol was reduced with icosapent ethyl, and reductions in c-reactive protein as a marker of inflammation were also noted. Both dose regimens were well tolerated, and there was an increase in arthralgia with icosapent ethyl.

The Reduction of Cardiovascular Events with Icosapent Ethyl – Intervention Trial (REDUCE-IT), studied 8,179 patients who were on statin therapy and had raised triglycerides. Subjects were randomised to 2 g of icosapent ethyl twice daily or a mineral oil containing placebo and followed for a median of 4.9 years (3). Two thirds of the subjects were enrolled on the basis of secondary prevention with established cardiovascular disease, and one third on the basis of primary prevention with diabetes plus another risk factor. The primary endpoint was a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularisation, unstable angina, and subjects were followed for a median of 4.9 years. The event rate was high at 22% in the placebo group and 17% in the treatment group, a statistically significant 25% relative risk reduction. A key secondary endpoint of MACE (cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke) was also significantly reduced.

The most commonly reported side-effects were gastrointestinal upset, headache, arthralgia and rash. Safety and adverse events reporting in REDUCE-IT showed no significant difference in overall rates of adverse events between

treatment and placebo arms. A significantly higher incidence of hospitalisation for atrial fibrillation or flutter, constipation and peripheral oedema (6.5 vs. 5.0% P=0.002) was observed in the intervention group.

Specific evidence for use in diabetes

The typical dyslipidaemia seen in people with type 2 diabetes includes raised triglycerides so it is not surprising that there were many subjects with diabetes in these safety and efficacy trials. 29% of subjects in MARINE and 73% of subjects in ANCHOR had diabetes. 58% of subjects in REMOVE-IT had diabetes at baseline and the results were similar for subjects with and without diabetes with a 23% reduction in the primary endpoint in the diabetes subgroup and a 27% reduction in those without diabetes.

Discussion

REDUCE-IT demonstrated further reductions in cardiovascular events when icosapent ethyl was added to patients who are on statins and have raised triglyceride concentrations. The results are similar to the larger open-label Japan EPA Lipid Intervention Study (JELIS) which compared a lower dose of EPA pro-drug (1.8g daily) in addition to background statin therapy in 18,645 subjects with placebo and demonstrated a 19% lower risk of major adverse cardiovascular events (4).

The reduction in the primary end-point in REDUCE-IT cannot be explained by the reduction in triglyceride level alone as this would equate to an 8% reduction rather than the 25% risk reduction that was observed. While a reduction in CRP as a marker of systemic inflammation was also reduced compared with baseline, it is estimated that this would only equate to an additional 5% benefit in CV risk reduction.

A potential confounding factor is the choice of placebo, as mineral oil may promote the development of atherosclerosis or inflammation and is known to reduce the enteral absorption of other medications prescribed to mediate cardiovascular risk so theoretically this could have increased cardiovascular events in the control group. Similar trials in fish oil derivatives have also faced challenges in placebo selection due to the characteristic texture and aroma of the active drugs.

Other therapies which reduce triglyerides such as fibrates or niacin have conflicting evidence for overall cardiovascular benefit and utilisation is limited by significant side effect profiles and drug-interactions. The limited interactions and side-effect profile of icosapent ethyl make it an attractive option in the target patient population who are commonly on multiple additional medications. The results of further cardiovascular outcomes trials with n-3 fatty acids and fish oils are awaited with interest.

Declaration of interests

There are no conflicts of interest declared.

References

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Key Points

1. The n-3 fatty acid icosapent ethyl significantly reduced cardiovascular events when prescribed to people with diabetes or existing cardiovascular disease who were on statins and had raised triglycerides
2. Compared with other triglyceride-lowering therapy like niacin or fibrates icosapent ethyl has been proven to reduced cardiovascular events, has fewer interactions and less side-effects
3. The mechanism of benefit remains unclear and further evaluation and cardiovascular outcomes trials with n-3 fatty acids and fish oils are needed

Legend to figure.

Possible mechanisms of cardiovascular benefit of icosapent ethyl.