Bioavailability of Eicosapentaenoic and Docosahexaenoic n-3 Polyunsaturated Fatty Acids in Salmon Patties Compared with Capsules

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ABSTRACT: This sequential treatment trial compared the bioavailability of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) from salmon patties fortified with fish oil (DHA:EPA ratio = 1.8, total DHA + EPA about 2.2 g), unfortified salmon patties (DHA:EPA ratio = 1.9, total DHA + EPA about 1.1 g), and fish oil capsules (DHA:EPA ratio = 1.6, total DHA + EPA = 500 mg) in healthy older adults. Fortified salmon patties produced a significantly higher mean incremental area under the curve ($AUC_{fasting\text{-}9\ h}$) than unfortified patties for plasma EPA (37.6 in contrast to 12.9 μg·h/mL, $p = 0.017$), for plasma DHA (103.7 in contrast to 40.8 μg·h/mL, $p = 0.035$) and for plasma EPA + DHA (141.2 in contrast to 53.7 μg·h/mL, $p = 0.031$). Plasma EPA and DHA responses were larger with the fortified than the unfortified patties, indicating that fish oil incorporated into the salmon patties was bioavailable.

Keywords: n-3 fatty acids, bioavailability, eicosapentaenoic acid, docosahexaenoic acid, enrichment

Introduction

THE N-3 POLYUNSATURATED FATTY ACIDS EICOSAPENTAENOIC ACID (EPA) and docosahexaenoic acid (DHA) are precursors of metabolic products with important roles in blood clotting, immune response, and vascular tone (Kinsella and others 1990; Simopoulos 1991). These n-3 fatty acids are essential for normal growth and development throughout the life cycle, and they should be components of the diets of all persons. In addition, a higher intake of n-3 fatty acids may have a beneficial role in the prevention or treatment of diseases, such as coronary heart disease (Krauss and others 2000), hypertension, autoimmune disorders (Connor 1997; Kremer and others 1997), cancer (Simopoulos 1991), and diabetes (Prince and Deeg 1997).

It is increasingly evident that incorporation of greater amounts of n-3 fatty acids into the diet, through eating fish or consuming fish oil supplements, may aid in the prevention of various diseases (Simopoulos 1991; Kremer and others 1997; Lovegrove and others 1997; Prince and Deeg 1997; Krauss and others 2000). A variety of cold-water marine fish oils (cod liver oil, salmon oil, tuna oil, menhaden oils) have been available to consumers for many years as dietary supplements, and now preparations containing either fish oils rich in EPA and DHA or highly concentrated preparations (ethyl esters) of EPA and DHA are available. Early studies indicated that the quantity of fish consumption required to reap therapeutic benefits was quite high—from 250 to 500 g fish per d (Bang and Dyerberg 1972; Bang and others 1975; Dyerberg and others 1975). More recent investigations suggest that lower levels also provide nutritional benefits (Harris 1997; Krauss and others 2000).

Several scientific organizations have made recommendations regarding optimal n-3 fatty acid consumption (Roche 1999; Krauss and others 2000). The recommendations vary widely (about a 7-fold difference), due in part to the differing definitions of optimal nutrition: "preventing deficiency" or "promoting health" (Roche 1999). In any case, the daily n-3 fatty acid intake of most persons falls short of these recommendations. Because of the numerous reports of the beneficial effects of increased n-3 fatty acid intake among persons with coronary artery disease (de Lorgeril and others 1999; von Schacky and others 1999; GISSI-Prevenzione Investigators 1999; Krauss and others 2000), the American Heart Association recently suggested consumption of one fatty fish meal per d (or alternately, a fish oil supplement) to achieve n-3 fatty acid intake of about 900 mg per d (Krauss and others 2000). Increasing fish intake is the most obvious way to increase n-3 fatty acid intake, but many individuals would prefer to consume fewer servings of fish or supplements, leading to the need for the development of new n-3 fatty acid products.

With the availability of new n-3 fatty acid products comes the question of whether or not these preparations are similar to fish and other fish oils in their absorption and efficacy (Davidson and others 1997; Morcos 1997; Vidgren and others 1997; Wallace and others 2000). The bioavailability of n-3 fatty acids from fish, fish oil, EPA/DHA supplements, and fish oil-enriched foods is affected by many variables including concomitant dietary factors and the type and form of fatty acid consumed (Meyer and others 1976; Lawson and Hughes 1988; Silverman and others 1991). The bioavailability of the n-3 fatty acids (EPA and DHA) is especially important given the need to add fish oils rich in these essential fatty acids to food products.

The primary objective of this study was to compare the bioavailability of n-3 fatty acids from salmon patties fortified with an EPA- and DHA-containing oil (ROPUFA® '30' n-3 FOOD Oil), unfortified salmon patties, and EPA/DHA capsules (ROPUFA® '30' n-3 FOOD Oil) administered with vegetable-based patties.

Materials and Methods

Study design

This was a sequential treatment study with 4 clinic visits: 1 at screening and 3 at which treatment was administered. Treatment visits were separated by 1-wk washout periods. The trial was conducted according to Good Clinical Practice, the 1996 Declaration of Helsinki, and United States Code of Federal Regulations Title 21, Part 50, Protection of Human Subjects, and Part 56, Institutional Review Boards. Signed written informed consent for the study was obtained from all subjects before protocol-specific procedures were

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Table 1—Fatty acid composition of ROPUFA® '30' n-3 FOOD Oil (EPA/DHA-containing fish oil)

Fatty acid	Formula	% by weight[a]
Myristic acid	C14:0	5.5
Palmitic acid	C16:0	16.3
Palmitoleic acid	C16:1n-7	6.1
Stearic acid	C18:0	3.1
Oleic acid	C18:1n-9	11.6
cis-Vaccenic acid	C18:1n-7	2.6
Linoleic acid	C18:2n-6c	2.5
gamma-Linolenic acid	C18:3n-6	0.2
Eicosenoic acid	C20:1n-9	1.8
alpha-Linolenic acid	C18:3n-3	1.7
Moroctic/Stearidonic acid	C18:4n-3	2.9
Erucic acid	C22:1n-9	2.3
Arachidonic acid	C20:4n-6	0.9
Eicosapentaenoic acid (EPA)	C20:5n-3	11.0
Docosapentaenoic acid (DPA)	C22:5n-3	1.1
Docosahexaenoic acid (DHA)	C22:6n-3	17.6
Saturated fatty acids	—	28.4
Monounsaturated fatty acids	—	25.8
Polyunsaturated fatty acids	—	39.4
Total uncharacterized	—	6.3
n-3 fatty acids	—	35.0
DHA:EPA ratio	—	1.6

aValues are the mean of analyses of 8 production lots.

Table 2—Macronutrient composition of study product sandwiches and capsules

	Unfortified salmon patties (Control)	Fortified salmon patties	Vegetable patties + capsules
Patties			
Energy (kcal)	220	248	225
Fat (g)	4.2	7.2	1.3
Protein (g)	42	42	40
Carbohydrate (g)	8	8	17.5
Bun(s)			
Energy (kcal)	165	165	110
Fat (g)	1.5	1.5	1
Protein (g)	6	6	4
Carbohydrate (g)	30	30	20
Butter			
Energy (kcal)	27	0	36
Fat (g)	3.1	0	4.1
Protein (g)	0	0	0
Carbohydrate (g)	0	0	0
Capsules			
Energy (kcal)	0	0	27
Fat (g)	0	0	3
Protein (g)	0	0	0
Carbohydrate (g)	0	0	0
TOTAL			
Energy (kcal)	412	413	398
Fat (g)	9	9	9
Protein (g)	48	48	44
Carbohydrate (g)	38	38	38

carried out. The protocol and consent form were approved by Schulman Associates Institutional Review Board Inc. (Cincinnati, Ohio, U.S.A.).

Subjects

Subjects were recruited from the Chicago metropolitan area, utilizing the patient database of the Chicago Center for Clinical Research. Participants were men and women of non-childbearing potential (naturally or surgically postmenopausal), between the ages of 45 and 75 y. Eligible subjects were required to abstain from fish consumption for 1 wk prior to the 1st treatment visit and throughout the trial. All were apparently healthy, based on medical history, brief physical examination, and routine laboratory tests (serum chemistry, hematology, and urinalysis) conducted at the screening visit. Persons with serum triglyceride concentration above 250 mg/dL were excluded, as were those with a history of fish consumption of more than once per wk. Other exclusion criteria included clinical evidence of any significant chronic illness; history or presence of a clinically significant endocrine disorder; the presence of any manifest premalignant or malignant disease; and current unstable angina, congestive heart failure, inflammatory bowel disease, pancreatitis, diabetes, hypothyroidism, nephrotic syndrome, significant anemia, or hyperadrenocorticalism.

Because of the potential to interfere with the study results, use of any of the following medications was not allowed: oral hypolipidemic therapy within 4 wk prior to screening; use of unstable or cyclic doses of thiazides, beta-adrenergic blockers, thyroid hormones, quinidine, theophylline, or sex hormone replacement therapy; and a history or chronic use of systemic corticosteroids, androgens, or phenytoin.

Study products

Subjects consumed study products once at each of 3 treatment clinic visits. At the 1st treatment visit, subjects consumed a low-fat meal including 2 unfortified (control) salmon patties ("Salmon Burger," AquaCuisine Inc. of Boise, Idaho, U.S.A.: a processed patty made with natural Alaska salmon, potato starch, onion, breadcrumbs, water, brown rice syrup solids, seasonings, flavors, and colors). At the 2nd treatment visit, subjects received 2 salmon patties fortified with fish oil (ROPUFA® '30' n-3 FOOD Oil, Roche Vitamins Inc., Parsippany, N.J., U.S.A.) as part of a low-fat meal. Enrichment was achieved by incorporation of fish oil into the salmon patties during manufacture. At the 3rd treatment visit, subjects received 2.5 commercially available vegetable patties plus 3 fish oil capsules (ROPUFA® '30' n-3 FOOD Oil) as part of a low-fat meal.

The fish oil utilized in this study is a high-quality mixed species marine oil containing at least 30% n-3 polyunsaturated fatty acids in the form of triglycerides including EPA and DHA. A complete profile of the fatty acids in the marine oil is shown in Table 1. During the fish oil capsule treatment period, subjects took 3 capsules for a total dose of 500 mg EPA + DHA. Based on analyses of 5 randomly selected sample patties from each production lot, the EPA + DHA dose of the fortified salmon patty was approximately 1,144 mg per patty (total dose of about 2.2 g), and the unfortified salmon patty contained approximately 567 mg EPA + DHA per patty (total dose of about 1.1 g). The mean DHA:EPA ratios were 1.6, 1.9, and 1.8, for the capsules and unfortified and fortified patties, respectively.

Study products were administered as part of standardized, low-fat meals containing negligible amounts of n-3 fatty acids. Macronutrient composition of the fish oil capsule and salmon and vegetable-patty sandwich components of these meals is shown in Table 2. Subjects were asked to consume the entire meal, including study products, within 30 min. In addition to the treatment sandwich, all subjects were served 237 mL (8 oz) of unsweetened orange juice, 1 glass of water, and a 118 mL (4 oz) can of diced fruit cocktail in juice. Subjects were also offered 177 mL (6 oz) fat-free yogurt, clear sugar-free soft drink, fat-free saltines, soup, rice cakes, and an additional fruit cup after the 4-h blood sample. Decaffeinated coffee was also allowed at this point, but the only other beverages allowed were clear soft drink or water.

Table 3—Mean area under the curve ($AUC_{fasting\text{-}9\ h}$) plasma concentrations of EPA, DHA, and EPA + DHA according to treatment

	Unfortified salmon patties (control)	Fortified salmon patties	Vegetable patties + capsules
EPA, μg·h/mL	12.9 ± 6.5	37.6 ± 24.4[a]	5.9 ± 11.2[a]
DHA, μg·h/mL	40.8 ± 23.6	103.7 ± 77.0[a]	7.4 ± 12.1[a]
EPA + DHA, μg·h/mL	53.7 ± 29.1	141.2 ± 101.2[a]	13.4 ± 23.1[a]

[a]Superscripts in a row denote a statistically significant difference from the unfortified salmon patties (control) group by pairwise comparisons using the Dunnett's procedure ($p < 0.05$).

Assessments

The primary efficacy variable was the bioavailability of n-3 fatty acids (EPA and DHA), measured as the mean area under the curve (AUC) for triglyceride EPA and DHA in blood samples collected prior to consumption of study products (average of values obtained from measurements conducted on samples collected at –0.5 and 0 h) and at 1, 2, 4, 6, and 9 h following consumption of the low-fat meal plus study products.

EPA and DHA were measured in triglycerides, as described by Subbaiah and others (1993). Following lipid extraction, triglycerides were separated on silica gel TLC plates with the solvent system of hexane: diethyl ether: acetic acid (70: 30: 1, v/v), and the spot corresponding to standard triolein was scraped from the plate after spraying the plate with 0.1% dichlorofluorescein in 95% ethanol. Fatty acid methyl esters were prepared with the BF3-methanol reagent (Supelco, Bellefonte, Pa., U.S.A.) and were analyzed on a Shimadzu GC-9 chromatograph (Shimadzu Scientific Instruments Inc., Columbia, Md., U.S.A.) equipped with a SupelcoWax 10 fused-silica column (Supelco Inc., Bellefonte, Pa., U.S.A.). The temperature of the oven was initially 172 °C for 8 min, and was raised at a rate of 6 °C per min to a final temperature of 220 °C, which was maintained for 20 min. Peaks were identified by comparing with retention times of standards. The concentrations of DHA and EPA were calculated with reference to a 17:0 internal standard.

Safety and tolerability were assessed by monitoring adverse events reported by subjects at each clinic visit. Additionally, vital signs (blood pressure and pulse) and body weight were measured at each clinic visit.

Statistical methods

The per-protocol population, including all subjects who completed the full length of the study, was utilized for efficacy analyses. An analysis of variance model was generated to compare the incremental areas under the curve (fasting [average of values at –0.5 and 0 h] to 9 h), hereafter denoted as mean $AUC_{fasting\text{-}9\ h}$ of triglyceride EPA and DHA among the 3 treatment phases. Post-hoc pairwise comparisons were conducted utilizing Dunnett's procedure.

The safety population included all subjects who entered the study, had at least 1 treatment clinic visit, and received 1 dose of study product. Possible differences in the incidence of adverse events were assessed with the Fisher's exact test.

Results and Discussion

Subjects

Eleven subjects were randomized to this sequential treatment study, of which 10 (90.9%) completed. One subject withdrew from the study (withdrew consent) after the 2nd treatment clinic visit. All subjects followed the same treatment sequence (unfortified: fortifed: vegetable-patties plus capsules), which could be a potential criticism of the study, but this did not likely affect the results. The risk with nonrandom assignment would be a carry-over effect between treatment phases, indicated by a rising baseline as the study progresses. There was no increase in baseline values over time, suggesting that the washout period between treatments was sufficient. All randomized subjects were evaluated for safety, and the 10 subjects who completed all treatment clinic visits were evaluated for efficacy.

Subjects were predominantly Caucasian (8 [72.7%]). Three (27.3%) of the 11 subjects were black. Gender distribution was approximately equal: 5 (45.5%) subjects were male, and 6 (54.5%) were female, and the group had a mean age of 58.3 y. Because only one subject (black female, 53 y of age) dropped from the study, demographic characteristics of the 10 subjects who completed were similar to all subjects. Of the completed subjects, 80% and 20% were Caucasian or black, respectively. There was equal male and female distribution among this group, and the mean age was 58.8 y.

Incremental area under the curve

Results of the mean $AUC_{fasting\text{-}9\ h}$ EPA and DHA analyses are shown in Table 3. Pairwise comparisons utilizing Dunnett's procedure indicated that consumption of the fortified patties resulted in significantly higher plasma concentrations of EPA than consumption of the unfortified patties ($p = 0.017$). Additionally, consumption of the unfortified patties resulted in significantly higher concentrations of EPA than did the vegetable patties plus the capsules ($p = 0.013$). According to pairwise comparisons, the vegetable patties plus capsules produced significantly lower DHA concentrations than the unfortified patties ($p < 0.001$). The difference between fortified and unfortified patty responses was also significant ($p = 0.035$). Vegetable patties plus capsules were found to produce significantly lower plasma EPA + DHA concentrations than the unfortified patties ($p = 0.003$), and the difference between fortified and unfortified patties in the EPA + DHA mean $AUC_{fasting\text{-}9\ h}$ concentrations was also statistically significant ($p = 0.031$).

Because of differences in doses between groups, a direct comparison of the bioavailability of the n-3 fatty acids in the various treatments was not possible. However, qualitative evaluation is possible by looking at the proportionality of n-3 fatty acids consumed relative to the $AUC_{fasting\text{-}9\ h}$, which was 4.0 for the capsules compared to the unfortified patties, 10.5 for the capsules compared to the fortified patties, and 2.6 for the unfortified patties compared to the fortified patties. We would expect the $AUC_{fasting\text{-}9\ h}$ to be roughly proportional to the dose consumed, with the $AUC_{fasting\text{-}9\ h}$ smallest with the capsules, larger with the unfortified patties and the largest with the fortified patties, which was in fact what we saw. For DHA, there was an approximate 5-fold increase in the $AUC_{fasting\text{-}9\ h}$ for the unfortified patties compared to the capsules, and an additional 2.5-fold increase for the fortified compared to the unfortified patties. For EPA, these increases were about 2-fold and 3-fold, and for the total EPA + DHA increase in responses were approximately 4-fold and 2.5-fold. These results demonstrate that the fish oil n-3 fatty acids were biologically available when incorporated into salmon patties.

As mentioned, the current study did not allow a direct comparison of the bioavailability of n-3 fatty acids from fortified salmon patties as compared to a fish oil capsule, but another recent study examined the bioavailability of n-3 fatty acids from foods enriched with microencapsulated fish oil compared with n-3 fatty acids in a capsule (Wallace and others 2000). Analyses of platelet fatty acid composition following 4 wk of intervention indicated no significant difference in the bioavailability of n-3 fatty acids from foods as compared to capsules.

Generally, difficulties in comparing the bioavailability of various fish oils and n-3 fatty acid supplements have arisen due to the unspecified composition of the products being compared. Some fish oils are based on either ethyl ester or free acids, and may also vary greatly in their relative concentrations of EPA and DHA (Lawson and Hughes 1988; Childs and others 1990). Beckermann and others (1990) have reported that EPA and DHA are more bioavailable in the free fatty acid form and less bioavailable in the ethyl ester form as compared to ingestion as triglycerides. In the current study, the fish oil used was in triglyceride form, and the DHA:EPA ratio was similar among all products (1.6 in capsules, 1.9 in unfortified patties, and 1.8 in fortified patties).

Safety

All of the products examined were found to be safe and well tolerated. Only 2 subjects reported adverse events (a fall with mild abrasions during the fortified salmon patty period of the study and mild headache during the unfortified [control] salmon patty period). Both events were judged by the investigator not to be related to the study products. There were no remarkable changes in body weight or vital signs during the study. Mean systolic blood pressure at clinic visits (including baseline) ranged from 121.1 to 126.4 mm Hg, mean diastolic blood pressure ranged from 73.8 to 81.0 mm Hg, and mean pulse rate ranged from 69.4 to 78.2 beats per min. Mean body weight at each clinic visit (including baseline) ranged from 86.6 to 90.0 kg.

Conclusions

THE RESULTS OF THIS CLINICAL TRIAL INDICATE THAT INCORPORATION of EPA and DHA from fish oil into salmon patties is bioavailable, resulting in elevated plasma n-3 fatty acid concentrations. Although the quantity of fish consumption required to achieve nutritional benefits (preventing coronary heart disease, hypertension, and autoimmune diseases) remains to be defined, the results reported here suggest that persons who want to increase their n-3 fatty acid consumption may be able to do so with fewer servings of fish via n-3 enriched fish products, such as fish oil-fortified salmon patties.

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