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510 2 Chemical abstracts $x 0009-2258

525 Has annual supplements with titles: Cardiovascular surgery, 1962-, and: Abstracts, 1964- ; also has occasional additional supplements.
525 Supplements for 1962-63 and <1982 lack "supplement" in title.
525 Supplements for 1987- also called: Circulation monograph, no. 1-
555 Vols. 1-52, 1950-75. 1 v.
580 Some supplements also issued as: American Heart Association monograph, 1962-85; and, Monograph (American Heart Association), 1986.
580 Includes: Hypertension, v. 12 (published as Aug. 1964 supplement), which is also available separately.
588 Latest issue consulted: Vol. 107, no. 14 (Apr. 15, 2003).
650 0 Cardiology $v Periodicals.
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ATTACHMENT 2

(Grimsgaard)

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The American Journal of
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VOLUME 66 NUMBER 3 SEPTEMBER 1997

Original Research Communications

(continued)

Highly purified eicosapentaenoic acid and docosahexaenoic acid in humans have similar triacylglycerol-lowering effects but divergent effects on serum fatty acids[1–3]

Sameline Grimsgaard, Kaare H Bønaa, John-Bjarne Hansen, and Arne Nordøy

ABSTRACT To compare the effects of highly purified ethyl ester concentrates of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) on serum lipids, apolipoproteins, and serum phospholipid fatty acids in humans, we conducted a double-blind, placebo-controlled, parallel design intervention study. Healthy nonsmoking men (n = 234) aged 36–56 y were randomly assigned to dietary supplementation with 3.8 g EPA/d, 3.6 g DHA/d, or 4.0 g corn oil/d (placebo) for 7 wk. Serum triacylglycerols decreased 26% ($P < 0.0001$) in the DHA group and 21% ($P = 0.0001$) in the EPA group compared with the corn oil group. Although not significant, net decreases in serum triacylglycerols were consistently greater in the DHA group across all quartiles of baseline triacylglycerol concentrations. Serum high-density-lipoprotein cholesterol increased 0.06 mmol/L ($P = 0.0002$) in the DHA group. In the EPA group, serum total cholesterol decreased 0.15 mmol/L ($P = 0.02$) and apolipoprotein A-I decreased 0.04 g/L ($P = 0.0003$). In the DHA group, serum phospholipid DHA increased by 69% and EPA increased by 29%, indicating retroconversion of DHA to EPA. In the EPA group, serum phospholipid EPA increased by 297% whereas DHA decreased by 15%, suggesting that EPA is not elongated to DHA in humans. The serum phospholipid ratio of n−3 to n−6 fatty acids increased in both groups, whereas the relative changes in n−6 fatty acids suggested possible alterations in liver desaturation activity in the DHA group. We conclude that both DHA and EPA decrease serum triacylglycerols, but have differential effects on lipoprotein and fatty acid metabolism in humans. *Am J Clin Nutr* 1997;66:649–59.

KEY WORDS Fatty acids, n−3 fatty acids, eicosapentaenoic acid, docosahexaenoic acid, triacylglycerols, phospholipids, randomized controlled trials

INTRODUCTION

Accumulating evidence indicates that fish oil, rich in eicosapentaenoic acid (EPA; 20:5n−3) and docosahexaenoic acid (DHA; 22:6n−3) of the n−3 family, can modify a variety of cellular processes associated with lipid metabolism, atherosclerosis, hypertension, thrombosis, and inflammation (1). The amount and the ratio of DHA to EPA in different marine sources vary considerably (1, 2). Earlier studies of n−3 fatty acid supplementation in humans used oils varying in dosage form, total dose of fatty acids, and relative content of DHA and EPA. Examination of these data shows that the most consistent effect of n−3 fatty acids on cardiovascular disease risk factors is a reduction in serum triacylglycerol concentration, whereas reported effects on other variables are less consistent (3–5). It is possible that the inconsistencies derive from chance findings in small-scale studies or differences in study design. However, they may also be attributed to varying metabolic effects of DHA and EPA.

Animal studies showed that EPA and DHA accumulate in different compartments in the body and thus may be subject to differences in both metabolism and effects (6–8). DHA selectively attenuated expression of proatherogenic and proinflammatory proteins in human endothelial cells, suggesting a beneficial effect of DHA on atherosclerosis (9), whereas EPA may be a more potent platelet inhibitor than DHA (10, 11). In vitro studies indicate that EPA and DHA have different effects on triacylglycerol synthesis (12), and it was suggested that EPA is primarily responsible for the hypotriacylglycerolemic effect of n−3 fatty acids both in rats (13) and humans (14). The extent to which these reports can be generalized is constrained by limitations in study design, however. Knowledge of the specific effects of EPA and DHA is needed to target n−3 supplements for specific effects. Long-term studies with adequate sample size comparing the biological effects of pure DHA and EPA in human volunteers have not been reported (10, 14–16). We therefore conducted a double-blind, randomized, placebo-controlled, parallel design intervention study to evaluate effects of dietary supplementation with highly purified EPA or DHA on serum lipids, apolipoproteins, and serum phospholipid fatty acid composition.

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[2] Supported by grants from the Norwegian Research Council, Pronova Biocare AS, and Odd Berg Medical Research Foundation.

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SUBJECTS AND METHODS

Subjects and experimental design

In 1986–1987, 21 826 subjects, 81.3% of the men aged 20–61 y old and the women aged 20–56 y old living in the municipality of Tromsø, participated in a health survey (visit 1) (17). All subjects completed a questionnaire about previous disease, use of drugs, and diet and smoking habits, and their height, weight, blood pressure, and nonfasting serum lipid concentrations were measured. Four hundred seven men between the ages of 35 and 55 were selected according to the following criteria: they reported being healthy nonsmokers, did not use nonprescribed or prescribed drugs, and consumed less than four fish dishes per week in their usual diet. They also had serum cholesterol concentrations < 8.0 mmol/L, diastolic blood pressure < 95 mm Hg, and systolic blood pressure < 160 mm Hg. These men were then asked in 1993 to undergo a clinical examination that included a complete medical history, physical examination, and laboratory tests.

Among the 349 men who responded to the invitation, 251 subjects filled the above-mentioned criteria and were recruited into the present study. They had no cardiovascular, liver, or renal disease; bleeding disorder; diabetes mellitus; psychopathologic disease; alcoholism; or other disease that can influence blood pressure, lipid metabolism, or hemostasis. They were not consuming special diets and did not expect to change their diet or lifestyle during the study period. Their mean (± SD) age was 44 ± 5 y (range: 36–56). The study was approved by the regional board of research ethics, and each subject gave informed consent.

The study was performed according to Good Clinical Practice requirements (18). It began with a 4-mo run-in period during which subjects were asked to continue their usual diet and living habits and during which their blood pressure and fasting serum lipid concentrations were measured on two occasions (visit 2 and visit 3). Each subject's average intake of nutrients was calculated on a fourth visit. At the beginning of the run-in period and throughout the study, participants were instructed not to ingest cod liver oil or other fish-oil supplements.

For entry into the intervention phase of the study, a subject's mean serum triacylglycerol concentration during the run-in period had to be < 5.0 mmol/L and mean serum cholesterol concentration < 9.5 mmol/L. Among the 251 subjects, 2 were smokers, 2 had serum glucose or triacylglycerol concentrations above the inclusion criteria, 2 used cardiovascular drugs, 1 consumed more than three fish dishes per week, and 10 dropped out during the run-in period for personal reasons. Thus, 234 men entered the double-blind, parallel group intervention trial, which lasted for 7 wk. Computer-generated random numbers were used to assign the participants to either 4.0 g 95% ethyl ester EPA/d, 4.0 g 90% ethyl ester DHA/d, or 4.0 g corn oil/d. The dietary supplements were administered in indistinguishable soft gelatin capsules that each contained 1.0 g oil and 4–6 IU vitamin E as an antioxidant (**Table 1**). Each individual was asked to ingest two capsules in the morning and two capsules at night. The dietary supplements were manufactured by Pronova Biocare AS, Oslo.

Participants were examined after an overnight fast between 0800 and 1130 on two separate occasions separated by an interval of 3–5 d, both at baseline (visits 5 and 6) and after 7 wk of supplementation (visits 7 and 8). At each visit blood pressure was measured and blood samples were collected. Participants were asked to abstain from alcohol and strenuous exercise for 48 h before the visit. A telephone interview was performed in the middle of the intervention period to monitor study compliance, side effects, and intercurrent disease. Compliance was assessed by counting leftover capsules and was calculated as the percentage of the prescribed capsules taken. We also measured serum phospholipid fatty acid concentrations at baseline and at the end of intervention.

TABLE 1
Composition of dietary supplements[1]

Constituent	DHA	EPA	Corn oil
22:6n−3 Ethyl ester (mg)	889	12	0
20:5n−3 Ethyl ester (mg)	18	941	0
18:2n−6 (mg)	0	0	559
18:1n−9 (mg)	0	0	259
Vitamin E (IU)	4–6	4–6	3.7
p-Anisidine value	<35	<35	—
Peroxide value (mmol/g)	<0.01	<0.01	—

[1] Dietary supplements were given in indistinguishable, oblong, soft gelatin capsules of 1.4 g average weight. DHA, docosahexaenoic acid supplement; EPA, eicosapentaenoic acid supplement.

Clinical and laboratory measurements

Height was measured during the run-in period and weight was measured at baseline and after the intervention period on an electronic scale with subjects wearing light clothing and no shoes. Before the intervention each subject's habitual nutrient intake was assessed during a 1-h interview by a certified clinical nutritionist using the dietary history method. Food models and containers were used to estimate quantities. Dietary constituents were calculated from standard food tables that also cover individual fatty acids by using a specially designed computer program (19–22). Each subject completed a self-administered questionnaire at baseline and during the last week of the intervention to monitor food habits and physical activity during the intervention. Participants were asked how many times they ate fish or meat for dinner and how many units of alcohol they consumed during the past week (one unit of alcohol equals 9 g). Those who reported being physically active four or more times weekly for ≥ 20 min, leading to sweating or shortness of breath, were categorized as active; those reporting 1–3 times weekly were categorized as moderately active; and those reporting 0 times weekly were categorized as sedentary.

Blood samples were drawn from an antecubital vein into an evacuated tube system using minimal stasis. Serum was prepared by clotting whole blood in a glass tube (Becton Dickinson, Meylan Cedex, France) at room temperature for 1 h and then centrifuging the sample at 2000 × *g* for 15 min at 22 °C. One-milliliter aliquots of serum were transferred into sterile 2-mL cryovials (Corning, Park Ridge, IL), flushed with nitrogen, and stored at −70 °C. Blood for plasma preparation was collected into vacutainers (Becton Dickinson) containing 0.129 mol sodium citrate/L (blood:anticoagulant = 10:1). Plasma was prepared by centrifugation at 2000 × *g* for 15 min at 22 °C, transferred into sterile cryovials in aliquots of 1 mL,

flushed with nitrogen, and stored at −70 °C. All blood samples were analyzed after completion of the intervention period and before the randomization code was broken.

Serum lipids were analyzed on a Hitachi 737 Automatic Analyzer (Boehringer Mannheim, Mannheim, Germany) with reagents from the manufacturer. Total cholesterol was measured with an enzymatic colorimetric method (CHOD-PAP) and high-density-lipoprotein (HDL) cholesterol was assayed by the same procedure after precipitation of lower-density lipoproteins with heparin and manganese chloride. Serum triacylglycerol concentrations were determined with an enzymatic colorimetric test (GPO-PAP). Low-density-lipoprotein (LDL) cholesterol was calculated according to the Friedewald formula (23). Apolipoprotein A-I and apolipoprotein B-1 were measured immunochemically by rate nephelometry using the Array Protein System from Beckman Instruments Inc (Brea, CA).

Fatty acids were measured by extracting total lipids from 500 μL serum according to Folch et al (24), with phosphatidylcholine diheptadecanoyl added as an internal standard (P-5014; Sigma Chemical Company, St Louis), chloroform:methanol (2:1, by vol) as a solvent, and butylated hydroxytoluene (75 mg/L) as an antioxidant. Total phospholipids were separated by solid-phase extraction with NH_2 columns (size 3 cc; Analytiche Bond Elut LRC; Varian, Harbour City, CA) (25), followed by transmethylation with boron trifluoride, extraction into hexane, and evaporation to dryness. The fatty acid methyl esters were dissolved in hexane and analyzed by gas-liquid chromatography (Shimadzu GC-14 A; Shimadzu Corporation, Kyoto, Japan) fitted with a capillary column (CP-Sil 88; length: 50 m, internal diameter: 0.25 mm) obtained from Chrompack Inc (Raritan, NJ). Retention times and response factors for each fatty acid were determined using standards obtained from Nu-Chek Prep (Elysian, MN). The results were integrated on a Shimadzu C-R4A integrator. Fatty acid concentrations are reported as μmol fatty acid/L serum.

Statistical analysis

All results are expressed as means ± SDs. On examination of the frequency distributions, all variables except serum triacylglycerol and certain lifestyle factors such as level of physical activity and fish, meat, and alcohol consumption were normally distributed at baseline and at the end of intervention. Serum lipid concentrations at baseline and at the end of the intervention were calculated as the mean of the values obtained at visits 5 and 6 and the mean of the values obtained at visits 7 and 8, respectively. Change was calculated as the value obtained after intervention minus the value obtained at baseline. Percentage change was calculated as the group-wise mean percentage change from baseline. Because of missing values, change could not be calculated for some individuals. Analysis of changes in serum lipids, serum phospholipid 16:1n−7, and sum of serum phospholipid fatty acids are therefore based on 222, 217, and 209 subjects, respectively. Two influencing outlying values were excluded from the analysis of desaturation indexes.

To evaluate within-group change, we used paired *t* tests for normally distributed variables, the Wilcoxon signed-rank test for ordinal and non–normally distributed variables, and the chi-square statistic for categorical variables. One-way analysis of variance was used to evaluate whether change differed between groups; the *F* test was used for normally distributed variables and the Kruskal-Wallis test for ordinal and non–normally distributed variables. Between-group comparisons of change were done by contrasting groups in the SAS general linear model procedure when the overall *F* test was significant at $P < 0.05$ (26). We did not adjust for multiple comparisons (27). Results were considered significant when the two-sided *P* value was < 0.05. Caution should be applied when interpreting *P* values in the present study because three contrasts were tested. When applying the Tukey multiple-comparison procedure (28), the 95% CI included the null value of no effect for those contrasts for which the unadjusted *P* value was > 0.03. Correlations were tested by computing Pearson or Spearman correlation coefficients.

RESULTS

Three of the 234 subjects who were randomly assigned to a study arm dropped out during the intervention period. One subject in the DHA group was found to have fat intolerance after cholecystectomy, one subject in the EPA group developed diarrhea, and one subject in the corn oil group experienced vertigo and vomiting that was considered unrelated to the dietary supplements. Two individuals in the DHA group, three in the EPA group, and two in the corn oil group were excluded from the analysis. The reasons for exclusions were possible renal disease ($n = 1$), poor compliance with study protocol ($n = 1$), initiation of a vasoactive drug ($n = 1$), cancer surgery ($n = 1$), and change in amount of physical activity during the intervention ($n = 3$). Thus, 224 subjects are included in the present analysis. Mean ages of the subjects were 43 ± 5, 44 ± 5, and 45 ± 6 y and mean body mass indexes (in kg/m^2) were 24.9 ± 2.6, 25.6 ± 2.9, and 24.6 ± 2.7 in the DHA, EPA, and corn oil groups, respectively.

There were no significant changes in hematology, blood chemistry (electrolytes, alanine aminotransferase, γ-glutamyl transferase, alkaline phosphatase, albumin, bilirubin, creatinine, and C-reactive protein), serum glucose, or plasma-active renin after dietary intervention with DHA, EPA, or corn oil (data not shown).

Compliance and side effects

The mean number of days in the study was 49 ± 5, 48 ± 3, and 48 ± 4 d in the DHA, EPA, and corn oil groups, respectively. Percentage compliance was slightly poorer in the DHA group (91 ± 6%) compared with the EPA and corn oil groups (both 94 ± 6%). There were no within-group correlations between compliance and change in serum DHA, EPA, or linoleic acid concentrations.

Side effects were mild and transient and for most individuals faded 1–2 wk after the start of the intervention. Fifty-eight percent of subjects in the DHA group and 57% in the EPA group experienced belching after initiation of the dietary supplements compared with 4% in the corn oil group. A taste of fish oil during the intervention was reported by 67% of subjects in the DHA group, 65% in the EPA group, and 3% in the corn oil group.

Diet, body weight, and physical activity

The DHA, EPA, and corn oil groups were well balanced at baseline. Total fat accounted for 30% of energy intake in all

TABLE 2
Composition of background diet[1]

Daily nutrient intake	DHA (n = 72)	EPA (n = 75)	Corn oil (n = 77)
Energy (kJ)	10 370 ± 2561	10 223 ± 2170	10 877 ± 2455
Protein (g)	103 ± 23	103 ± 22	107 ± 25
Carbohydrate (g)	335 ± 80	324 ± 74	349 ± 87
Fiber (g)	24.1 ± 7.3	23.2 ± 6.7	25.2 ± 7.7
Alcohol (g)	5.82 ± 6.28	6.39 ± 6.56	7.04 ± 7.00
Total fat (g)	81.2 ± 32.1	81.6 ± 23.9	85.9 ± 27.0
Cholesterol (mg)	314 ± 102	327 ± 89	334 ± 101
Saturated fat (g)	33.6 ± 12.4	34.3 ± 10.9	35.4 ± 11.4
Monounsaturated fat (g)	27.6 ± 11.3	28.0 ± 8.7	29.6 ± 9.6
Polyunsaturated fat (g)	13.5 ± 8.4	12.7 ± 4.6	14.0 ± 6.1
P:S	0.40 ± 0.15	0.39 ± 0.13	0.40 ± 0.13
18:2n−6 (g)	10.2 ± 7.0	9.50 ± 3.70	10.7 ± 5.1
20:5n−3 (g)	0.18 ± 0.20	0.19 ± 0.18	0.19 ± 0.21
22:6n−3 (g)	0.34 ± 0.32	0.35 ± 0.28	0.36 ± 0.32
β-Carotene (μg)	2651 ± 1902	2634 ± 1284	2749 ± 1905
Retinol (μg)	1003 ± 955	993 ± 717	1031 ± 697
Thiamine (mg)	1.66 ± 0.38	1.67 ± 0.35	1.76 ± 0.43
Riboflavin (mg)	2.20 ± 0.70	2.29 ± 0.67	2.31 ± 0.72
Niacin (mg)	23.6 ± 4.8	23.2 ± 4.8	23.8 ± 5.2
Vitamin C (mg)	90.0 ± 1.6	78.6 ± 35.5	88.9 ± 45.0
Vitamin D (μg)	6.08 ± 9.77	5.33 ± 4.16	5.65 ± 3.81
Vitamin E (mg)	4.87 ± 1.48	4.96 ± 1.34	5.33 ± 1.53

[1] $\bar{x}$ ± SD. DHA, docosahexaenoic acid group; EPA, eicosapentaenoic acid group; P:S, ratio of polyunsaturated to saturated fatty acids.

groups. Dietary intake of DHA and EPA at baseline accounted for 0.7% of total fat intake. Differences in nutrient intake between the DHA, EPA, and corn oil groups were minor and not significant (**Table 2**). No significantly different within- or between-group changes were found with respect to body weight, physical activity, or food habits during the intervention (**Table 3**). Body weight increased by 0.6 kg in the corn oil group and by 0.7 kg in the DHA and EPA groups. There was a nonsignificant increase in the percentage of participants who reported being sedentary after compared with before the intervention. Alcohol, meat, and fish consumption (dinner meals) increased slightly but not significantly during the intervention. None of the participants reported consuming more than three fish dishes weekly before or during the intervention. There was good agreement between measures of alcohol consumption obtained by the nutritionist during the run-in period and by the self-administered questionnaire at baseline (r = 0.73, P = 0.0001).

Serum lipids and apolipoproteins

Serum mean (95% CI in parentheses) triacylglycerol concentrations decreased 0.22 mmol/L (0.15, 0.29) in the DHA group and 0.15 mmol/L (0.06, 0.24) in the EPA group (**Table 4**). In the corn oil group serum triacylglycerols increased 0.11 mmol/L (0.03, 0.19). Compared with change for the corn oil group, serum triacylglycerols decreased 26% in the DHA group and 21% in the EPA group. The difference between the DHA and EPA groups was not significant (P = 0.14). However, net decreases in serum triacylglycerols were consistently greater in the DHA group than in the EPA group across quartiles of baseline triacylglycerol concentrations (**Table 5**). In the EPA and DHA groups there were no correlations between changes in individual n−3 fatty acids and changes in serum triacylglycerol concentrations.

Serum total cholesterol decreased 0.15 mmol/L ($P < 0.05$) in the EPA group and apolipoprotein A-I decreased 0.04 g/L ($P <$ 0.001, Table 4). These changes differed significantly from both the DHA and the corn oil groups. In the DHA group, HDL cholesterol increased 0.06 mmol/L ($P < 0.001$), differing significantly from both the EPA and corn oil groups. Hence, in both the EPA and DHA groups there was an increase in the ratio of HDL cholesterol to apolipoprotein A-I and a decrease in the ratio of total cholesterol to HDL cholesterol.

Serum phospholipid fatty acid concentrations

In the total study group (n = 224), the correlations between dietary intake and serum phospholipid concentrations of DHA and EPA at baseline were r = 0.39 and r = 0.35, respectively (both P = 0.0001). The mean of individual ratios of dietary DHA to EPA at baseline was 2.5 ± 1.2, whereas the serum phospholipid ratio of DHA to EPA was 3.8 ± 1.6 (P = 0.0001, for the difference between the ratios), indicating accumulation of DHA relative to EPA in serum phospholipids.

TABLE 3
Body weight and lifestyle factors at baseline and change after 7 wk of supplementation with docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), or corn oil[1]

	DHA (n = 72)		EPA (n = 75)		Corn oil (n = 77)	
	Baseline	Change	Baseline	Change	Baseline	Change
Body weight (kg)	80.0 ± 10.0[2]	0.7 ± 1.2	82.6 ± 10.0	0.7 ± 1.4	79.5 ± 9.4	0.6 ± 1.1
Fish consumption (dishes/wk)	2.10 ± 1.01	0.06 ± 1.13	2.16 ± 1.05	0.16 ± 1.06	2.03 ± 1.10	0.21 ± 1.29
Meat consumption (dishes/wk)	2.46 ± 1.31	0.24 ± 1.53	2.56 ± 1.39	0.16 ± 1.23	2.93 ± 1.28	0.15 ± 2.01
Teetotalers (%)	4	0	1	0	4	0
Alcohol consumption (g/wk)[3]	45.3 ± 44.3	0.3 ± 5.1	59.6 ± 63.9	−0.8 ± 6.5	55.5 ± 50.8	1.5 ± 7.0
Physical activity						
Sedentary (%)	22	3	26	1	25	6
Moderate (%)	69	−6	59	−1	54	1
Active (%)	9	3	15	0	21	−7

[1] There were no significant differences among groups.
[2] $\bar{x}$ ± SD.
[3] Teetotalers were excluded from analysis of alcohol consumption.

TABLE 4
Serum lipids and apolipoproteins at baseline and change after 7 wk of supplementation with docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), or corn oil

	DHA (n = 72)		EPA (n = 75)		Corn oil (n = 77)			Contrasts between groups: P		
	Baseline	Change	Baseline	Change	Baseline	Change	F test: P[1]	DHA vs EPA	DHA vs corn oil	EPA vs corn oil
Triacylglycerols (mmol/L)	1.24 ± 0.58[2]	−0.22 ± 0.31[3]	1.23 ± 0.57	−0.15 ± 0.40[4]	1.22 ± 0.55	0.11 ± 0.34[4]	0.0001	0.14	0.0001	0.0001
Total cholesterol (mmol/L)	6.00 ± 0.95	0.03 ± 0.49	5.98 ± 0.94	−0.15 ± 0.55[5]	6.02 ± 1.08	0.10 ± 0.55	0.01	0.04	0.4	0.004
LDL cholesterol (mmol/L)	4.06 ± 0.86	0.07 ± 0.46	4.06 ± 0.83	−0.08 ± 0.48	4.04 ± 0.98	0.06 ± 0.48	0.10	—	—	—
HDL cholesterol (mmol/L)	1.36 ± 0.30	0.06 ± 0.13[3]	1.33 ± 0.31	0.01 ± 0.12	1.41 ± 0.28	−0.01 ± 0.11	0.001	0.009	0.0005	0.4
Apolipoprotein A-I (g/L)	1.38 ± 0.21	0.02 ± 0.13	1.38 ± 0.20	−0.04 ± 0.10[3]	1.46 ± 0.23	0.00 ± 0.12	0.003	0.0008	0.3	0.02
Apolipoprotein B (g/L)	1.00 ± 0.21	−0.01 ± 0.11	1.01 ± 0.23	−0.03 ± 0.11[5]	1.02 ± 0.28	0.02 ± 0.11	0.05	—	—	—
HDL:apolipoprotein A-I	0.97 ± 0.14	0.04 ± 0.07[3]	0.96 ± 0.13	0.04 ± 0.08[3]	0.97 ± 0.12	−0.01 ± 0.06	0.0001	0.8	0.0003	0.0001
Total:HDL cholesterol	4.62 ± 1.19	−0.19 ± 0.52[4]	4.70 ± 1.24	−0.13 ± 0.47[5]	4.43 ± 1.19	0.11 ± 0.62	0.002	0.4	0.0006	0.007

[1] ANOVA for between-group comparisons of change.
[2] $\bar{x}$ ± SD.
[3–5] One-sample t test of difference between baseline and 7 wk: [3] $P < 0.001$, [4] $P < 0.01$, [5] $P < 0.05$.

TABLE 5
Change in serum triacylglycerol concentration in docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), and corn oil groups according to quartiles of baseline triacylglycerol concentration

Baseline triacylglycerol concentration	Change in serum triacylglycerol concentration			Estimated n−3 fatty acid effect[1]	
	DHA (n = 72)	EPA (n = 75)	Corn oil (n = 77)	DHA	EPA
	mmol/L			*mmol/L (%)*	
1st quartile:					
0.69 (0.34–0.82) mmol/L[2]	0.00 ± 0.13[3]	0.03 ± 0.21	0.10 ± 0.21	−0.10 (−14)	−0.07 (−10)
2nd quartile:					
0.96 (0.83–1.09) mmol/L	−0.14 ± 0.18	−0.04 ± 0.26	0.15 ± 0.28	−0.29 (−30)	−0.19 (−20)
3rd quartile:					
1.24 (1.10–1.44) mmol/L	−0.16 ± 0.23	−0.03 ± 0.34	0.14 ± 0.32	−0.30 (−24)	−0.17 (−14)
4th quartile:					
2.01 (1.45–3.61) mmol/L	−0.56 ± 0.35	−0.52 ± 0.46	0.03 ± 0.50	−0.59 (−29)	−0.55 (−27)

[1] Effect attributable to DHA and EPA; ie, change in DHA group minus change in corn oil group and change in EPA group minus change in corn oil group.
[2] $\bar{x}$; range in parentheses.
[3] $\bar{x}$ ± SD.

The total amount of serum phospholipid fatty acids did not change between groups during EPA, DHA, or corn oil supplementation (**Table 6**). Likewise, there were no changes in serum phospholipid saturated fatty acids. As for the monounsaturated fatty acids, palmitoleic acid (16:1n−7) decreased significantly by 20% in the DHA group, compared with no change in the EPA or corn oil groups. Oleic acid (18:1n−9) concentrations decreased by 11% and 12% in the DHA and EPA groups, respectively.

The total serum phospholipid n−6 fatty acid concentration (sum of 18:2n−6, 20:3n−6, and 20:4n−6) decreased more in the EPA (−23%) than in the DHA (−11%) group. In the DHA group, however, the ratio between the individual n−6 fatty acids changed more than in the EPA group. The ratio of 20:4n−6 + 20:3n−6 to 18:2n−6 can be used as an index of Δ6 desaturation activity because changes in Δ5 desaturation will not influence the ratio. The Δ6 desaturation index decreased significantly in the DHA group compared with no change in the EPA or corn oil group (**Table 7**). Similarly, the ratio of 20:4n−6 to 20:3n−6 + 18:2n−6 can be used as an index of Δ5 desaturation activity. This ratio decreased significantly in the DHA group whereas it increased significantly in the EPA group. As a result, the ratio of arachidonic (20:4n−6) to linoleic (18:2n−6) acid decreased in the DHA group and increased in the EPA group.

During the intervention, the serum phospholipid concentration of n−3 fatty acids increased by 47% in the DHA group and by 68% in the EPA group. The concentration of α-linolenic acid (18:3n−3) decreased in both the DHA and EPA groups compared with the corn oil group (Table 6). In the DHA group, mean serum phospholipid DHA and EPA concentrations increased significantly by 69% (individual range: −33% to 669%) and 29% (individual range: −63% to 557%), respectively, whereas docosapentaenoic acid (DPA; 22:5n−3) decreased by 33% (individual range: −72% to 221%). In this group, the correlation between the change in serum DHA and EPA was $r = 0.30$ ($P = 0.01$, **Figure 1**). In the EPA group, serum phospholipid EPA increased by 297% (individual range: −2% to 1196%) and docosapentaenoic acid by 130% (individual range: −9% to 393%). Surprisingly, the serum phospholipid concentration of DHA decreased by 15% (individual range: −65% to 85%; $P < 0.001$) after EPA supplementation. The correlation between the change in serum DHA and EPA was $r = 0.39$ ($P = 0.0005$) during supplementation with EPA (**Figure 2**).

DISCUSSION

Numerous studies have examined the effects of marine n−3 fatty acids on lipid metabolism, but the separate effects of the two major n−3 fatty acids have remained largely unknown. The present report extends previous data by showing that both DHA and EPA lower serum triacylglycerol concentrations. DHA may be responsible for the increase in HDL cholesterol observed with some n−3 fatty acid supplements whereas EPA may produce a small decrease in serum total cholesterol. Our data further show that DHA and EPA produce different effects on the fatty acid composition of serum phospholipids. We studied a fairly large sample recruited from the general population and compliance with the study protocol was good. The generalizability of the study therefore appears sound.

It is well established that n−3 fatty acids lower serum triacylglycerols, but this is the first study in humans showing that this effect is attributable to both EPA and DHA. Surprisingly, DHA consistently had a more pronounced triacylglycerol-lowering effect than EPA across all baseline concentrations of triacylglycerol (Table 5). These observations provide strong evidence that DHA has a triacylglycerol-lowering effect of its own and is not acting solely after retroconversion to EPA, because if that were the case, DHA would not be more potent than EPA. This finding contrasts with previous studies in rats, in which dietary supplementation of highly purified EPA lowered serum triacylglycerols whereas DHA had a modest effect if any (13, 29–31). The opposing findings may be dose related: the DHA and EPA supplements in the rat studies calculated as $mg \cdot d^{-1} \cdot kg\ body\ wt^{-1}$ are 10- to 30-fold larger than in the present study in humans (13, 29). The opposing findings may also depend on species differences because rats and humans differ with respect to lipid metabolism (32). Our finding is further opposed by results from a single-blind crossover study concluding that EPA is responsible for the triacylglycerol-lowering effect in humans (14). However, the study was small with only nine individuals in the DHA group, and the wash-out period was 2 wk, which is too short in dietary intervention trials with n−3 fatty acids (33).

Previous studies suggested that serum HDL cholesterol is better maintained with oil rich in DHA than oil rich in EPA (2, 34). The present data confirm these findings. The mechanism by which DHA increases HDL is not known. Serum triacylglycerols and HDL cholesterol were inversely correlated at baseline ($r = -0.42$, $P = 0.0001$), possibly due to plasma lipid transfer protein activity (35, 36). Interestingly, there was no correlation between changes in triacylglycerols and changes in HDL concentrations during supplementation with DHA ($r = -0.04$, $P = 0.73$), suggesting that DHA affects triacylglycerol and HDL metabolism through separate mechanisms. Much evidence indicates that n−3 fatty acids decrease serum triacylglycerols mainly by reducing hepatic very-low-density-lipoprotein (VLDL) synthesis and secretion (37, 38), but n−3 fatty acids may also increase the catabolic rate of VLDL (39). Moreover, it has been reported that lipid transfer protein activity decreased after n−3 fatty supplementation in humans (40), resulting in higher HDL-cholesterol concentrations and more triacylglycerols remaining in the VLDL fraction. Whether such effects can explain the increase in HDL cholesterol and the more pronounced triacylglycerol-lowering effect after DHA supplementation in the present study remains unknown.

In both groups receiving active treatment there was an increase in the ratio of HDL to apolipoprotein A-I. The finding suggests an increased surface to core ratio of the HDL molecule and a redistribution of the HDL subclasses toward the larger and more favorable HDL_2 as previously reported (34, 40, 41). Apparently, both n−3 fatty acids produce more cholesterol-rich HDL particles, DHA by increasing the HDL-cholesterol concentration and EPA by decreasing the apolipoprotein A-I concentration. In these healthy men with moderately high serum cholesterol concentrations, no convincing effects on total cholesterol were seen in either treatment group, although a 3%

TABLE 6
Serum phospholipid fatty acid concentration at baseline and change after 7 wk of supplementation with docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), or corn oil

	DHA (n = 72)		EPA (n = 75)		Corn oil (n = 77)			Contrasts between groups: P		
Fatty acid	Baseline	Change	Baseline	Change	Baseline	Change	F test: P[1]	DHA vs EPA	DHA vs corn oil	EPA vs corn oil
	μmol/L		*μmol/L*		*μmol/L*					
16:0	1450 ± 223[2]	−8 ± 168	1448 ± 221	−32 ± 174	1502 ± 290	16 ± 211	0.3	—	—	—
18:0	531 ± 113	−4 ± 77	524 ± 96	4 ± 77	543 ± 95	11 ± 83	0.5	—	—	—
16:1n−7	23.6 ± 10.9	−4.8 ± 11.7[3]	23.9 ± 18.0	−1.1 ± 13.1	28.1 ± 40.1	−4.8 ± 31.1	0.5	—	—	—
18:1n−9	344 ± 88	−37 ± 95[4]	340 ± 88	−41 ± 74[3]	348 ± 97	6 ± 90	0.001	0.8	0.003	0.001
22:1n−9	2.03 ± 3.31	−0.42 ± 3.41	2.34 ± 3.31	0.03 ± 2.51	1.79 ± 2.86	−0.13 ± 3.15	0.7	—	—	—
24:1n−9	74.5 ± 27.1	−0.5 ± 16.0	72.3 ± 24.9	−1.9 ± 18.5	75.9 ± 27.0	0.42 ± 24.76	0.8	—	—	—
18:2n−6	845 ± 185	−74 ± 184[4]	867 ± 168	−199 ± 128[3]	902 ± 160	21 ± 159	0.0001	0.0001	0.003	0.0001
20:3n−6	102 ± 32	−24 ± 26[3]	105 ± 29	−32 ± 23[3]	104 ± 32	7 ± 28[5]	0.0001	0.046	0.0001	0.0001
20:4n−6	253 ± 73	−39 ± 49[3]	260 ± 71	−48 ± 46[3]	261 ± 65	8 ± 52	0.0001	0.3	0.0001	0.0001
18:3n−3	7.72 ± 3.78	−1.13 ± 4.23[5]	8.30 ± 4.69	−2.07 ± 5.13[3]	7.66 ± 3.71	0.32 ± 4.00	0.005	0.2	0.05	0.001
20:5n−3	59.8 ± 53.7	17.6 ± 52.9[4]	61.4 ± 41.0	182.1 ± 91.1[3]	64.0 ± 40.3	−2.0 ± 40.7	0.0001	0.0001	0.07	0.0001
22:5n−3	32.0 ± 11.8	−10.6 ± 9.9[3]	33.9 ± 10.8	44.2 ± 25.8[3]	36.2 ± 10.2	1.6 ± 10.3	0.0001	0.0001	0.0001	0.0001
22:6n−3	185 ± 88	128 ± 87[3]	184 ± 65	−28 ± 48[3]	203 ± 69	−2 ± 52	0.0001	0.0001	0.0001	0.01
Sum of fatty acids[6]	4117 ± 653	−100 ± 481	4102 ± 600	−142 ± 485[5]	4326 ± 696	55 ± 594	0.06	—	—	—
n−3:n−6[7]	0.24 ± 0.12	0.16 ± 0.16[3]	0.24 ± 0.10	0.28 ± 0.17[3]	0.25 ± 0.09	−0.01 ± 0.07	0.0001	0.0001	0.0001	0.0001

[1] ANOVA for between-group comparisons of change. [2] $\bar{x}$ ± SD. [3–5] One-sample t test of difference between baseline and 7 wk: [3] $P < 0.001$, [4] $P < 0.01$, [5] $P < 0.05$. [6] Sum of fatty acids also includes 20:0, 22:0, 24:0, 20:1, 20:2, and 22:4n−6. [7] n−3:n−6 = [(18:3n−3 + 20:5n−3 + 22:5n−3 + 22:6n−3)/(18:2n−6 + 20:3n−6 + 20:4n−6)].

TABLE 7
Desaturation indexes at baseline and change after 7 wk of supplementation with docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), or corn oil

	DHA (n = 71)		EPA (n = 75)		Corn oil (n = 77)			Contrasts between groups: P		
Index	Baseline	Change	Baseline	Change	Baseline	Change	F test: P[1]	DHA vs EPA	DHA vs corn oil	EPA vs corn oil
Δ9 Desaturation index										
18:1n−9 to 18:0	0.65 ± 0.12[2]	−0.07 ± 0.14[3]	0.66 ± 0.15	−0.08 ± 0.11[3]	0.64 ± 0.12	0.01 ± 0.12	0.0001	0.8	0.0001	0.0001
16:1n−9 to 16:0	0.016 ± 0.006	−0.003 ± 0.007[3]	0.016 ± 0.013	0.000 ± 0.01	0.016 ± 0.018	−0.001 ± 0.010	0.1	—	—	—
Δ6 Desaturation index[4]	0.42 ± 0.10	−0.04 ± 0.09[3]	0.43 ± 0.12	0.00 ± 0.10	0.41 ± 0.10	0.01 ± 0.06	0.0006	0.0009	0.0007	0.9
Δ5 Desaturation index[5]	0.27 ± 0.07	−0.02 ± 0.06[6]	0.27 ± 0.07	0.02 ± 0.06[7]	0.26 ± 0.07	0.00 ± 0.04	0.0003	0.0001	0.08	0.02
Arachidonic:linoleic acid	0.30 ± 0.08	−0.02 ± 0.07[7]	0.31 ± 0.09	0.02 ± 0.07[6]	0.29 ± 0.08	0.00 ± 0.05	0.0007	0.0001	0.03	0.09

[1] ANOVA for between-group comparisons of change. [2] $\bar{x}$ ± SD. [3,6,7] One-sample t test of difference between baseline and 7 wk: [3] $P < 0.001$, [6] $P < 0.05$, [7] $P < 0.01$. [4] Δ6 Desaturation index = [(20:4n−6 + 20:3n−6)/18:2n−6]. [5] Δ5 Desaturation index = [20:4n−6/(20:3n6 + 18:2n−6)].

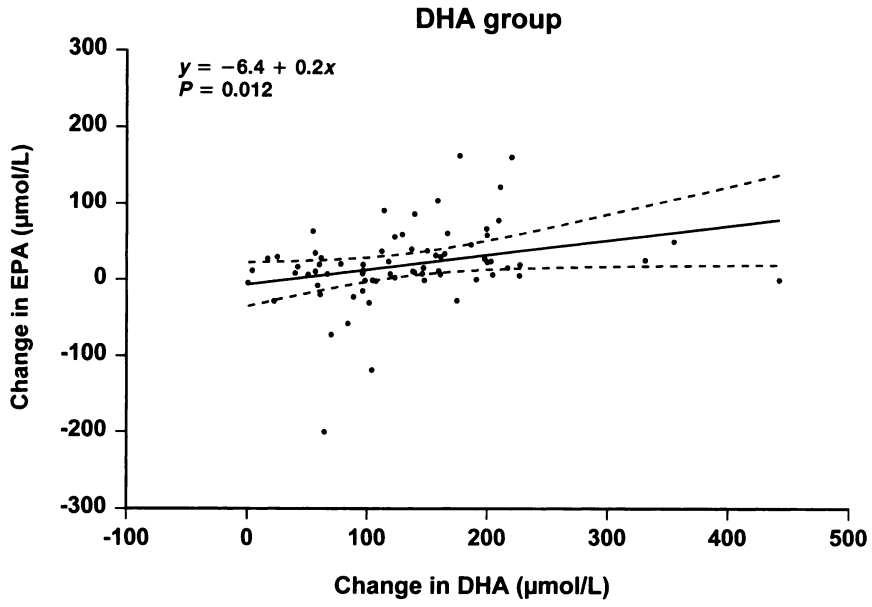

FIGURE 1. Plot of change in serum phospholipid docosahexaenoic acid (DHA) concentration versus change in serum phospholipid eicosapentaenoic acid (EPA) concentration in the DHA supplementation group (n = 72).

decrease was observed in the EPA group. This is in agreement with results obtained in previous studies concluding that n−3 fatty acids in moderate doses do not influence total cholesterol concentrations (4). There was, however, a beneficial decrease in the ratio of total cholesterol to HDL cholesterol in both the EPA and DHA groups.

Supplements with EPA or DHA produced an increase of serum phospholipid n−3 fatty acids at the expense of n−6 and monounsaturated fatty acids. In the EPA group, the percentage increase in serum phospholipid EPA (297%) was much larger than the corresponding increase in serum phospholipid DHA (69%) in the DHA group. A previous study showed that marine

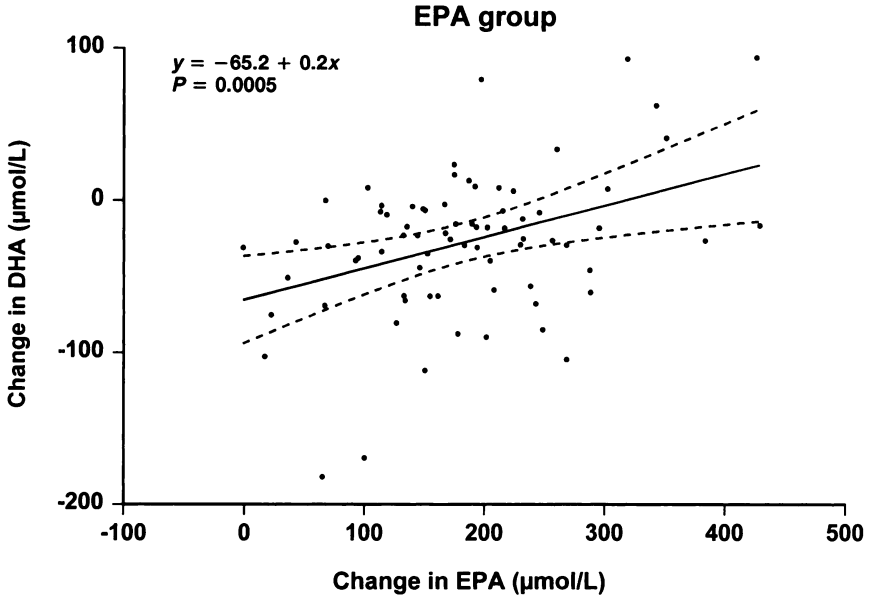

FIGURE 2. Plot of change in serum phospholipid eicosapentaenoic acid (EPA) concentration versus change in serum phospholipid docosahexaenoic acid (DHA) concentration in the EPA supplementation group (n = 75).

oil supplementation produced a rapid increase in plasma EPA that soon reached a plateau, whereas DHA concentration increased slowly and progressively (33). One might speculate that ingested EPA is more readily absorbed than DHA. Nevertheless, the observed ratio of DHA to EPA in serum phospholipids at baseline exceeded that of dietary intake (3.8 compared with 2.5, $P = 0.0001$).

In a metabolic study comparing ingestion of highly purified DHA and EPA, the two fatty acids produced identical increases in plasma chylomicron n−3 concentrations, but DHA was more rapidly cleared from plasma than was EPA (JB Hansen, personal communication, 1996). DHA is known to accumulate in the central nervous system and in cardiac tissue, and advanced atherosclerotic plaques are enriched with more DHA than EPA after dietary supplementation (42). These results indicate that the two fatty acids are distributed into different compartments of the body and have different metabolic actions. The present study supports the proposed pattern of incorporation in which DHA is selectively incorporated into extracirculatory pools whereas EPA has priority in the circulatory pool.

In the DHA group, the content of both DHA and EPA increased in serum phospholipids, indicating retroconversion of DHA to EPA. The degree of retroconversion appeared to be modest and may reach a saturation point (Figure 1). Similar findings were reported in cell and animal studies (11, 31) as well as in humans after dietary supplementation with highly purified EPA and DHA (10, 15, 16, 43). Theoretically, the increase of serum EPA in the DHA group could result from the small amount of EPA present in the DHA supplements (0.072 g/d). To examine this possibility, we did a regression analysis with dietary intake of EPA as the predictor variable and baseline serum phospholipid EPA concentration as the dependent variable (serum phospholipid EPA = 46.6 + 81.5 multiplied by dietary intake; $F = 0.0001$). The model predicted that the amount of extra EPA provided by the DHA supplement would increase serum phospholipid EPA to 67.8 mmol/L (95% CI: 60.4, 75.2) in the DHA group. The concentration of EPA after DHA supplementation (77.4 mmol/L) was higher, however, suggesting that retroconversion of DHA to EPA took place. Hence, ingested DHA may serve as a reservoir for EPA.

In the EPA group, there was a substantial increase in serum EPA and DPA whereas DHA decreased. This finding suggests that purified EPA is elongated to DPA, but not to DHA, and confirms previous studies in both rats and humans (10, 15, 16, 31). It is possible that EPA displaces DHA from the 2-position in serum phospholipids. Nevertheless, DHA concentrations increased modestly (20%) in 14 participants in the EPA group (Figure 2). This subgroup was characterized by large increases in both EPA (360%) and DPA (189%) during the intervention. Although not detectable from their dietary habit records, it may be that these individuals increased their fish consumption and consequently their DHA concentrations increased during intervention. An alternative explanation is that some DHA production takes place when EPA and DPA concentrations increase substantially.

A recent report established that DHA is biosynthesized from α-linolenic acid in human infants, although the conversion rate may be inadequate to support infant needs (44). Thus, α-linolenic acid and EPA may have different metabolic pathways because it seems that humans are not capable of synthesizing DHA from EPA unless the EPA concentration is high. This may have clinical importance if the purpose of n−3 fatty acid supplementation is to increase DHA concentration.

The change in the ratio of n−3 to n−6 serum phospholipid fatty acids was larger in the EPA group than in the DHA group. The proposed beneficial effects of n−3 fatty acids on cardiovascular disease have been partly attributed to an increase in the ratio of n−3 to n−6 fatty acids in cell membranes, resulting in a shift in eicosanoid synthesis toward a more vasodilatory and antiaggregatory state (5). In this study, the arachidonic acid concentration decreased similarly in the EPA and DHA groups. In the DHA group, however, the ratios (ie, desaturation indexes) of the individual n−6 fatty acids changed more than in the EPA group. Bearing in mind that serum phospholipid fatty acids are influenced by several factors, one might speculate that EPA and DHA have different effects on liver desaturation enzymes. Apparently, EPA exerts no effects on liver desaturation activity, suggesting that arachidonic acid decreased as a result of displacement from serum phospholipids. In the DHA group however, the decrease in arachidonic acid concentration may have resulted from decreased Δ6 and Δ5 desaturation. These enzymes are influenced by several factors including diet (45). n−3 Fatty acids decrease Δ6 and Δ5 desaturation in rats (46–48) and DHA in particular has been held responsible for reducing Δ6 desaturation, possibly by a feedback mechanism (31). The present data suggest that n−3 fatty acids may influence eicosanoid synthesis both by reducing arachidonic acid synthesis (DHA) and by displacing arachidonic acid from serum phospholipids (EPA).

In both the EPA and DHA groups there was a reduction in monoenes. This may represent a reduction in Δ9 desaturation as judged by the ratios of 18:0 to 18:1n−9 and of 16:0 to 16:1n−7. Similar observations were made in rats after supplementation with n−3 fatty acids (48, 49). Hence, n−3 fatty acids may affect membrane structure and function by altering activity in Δ9, Δ6, and Δ5 desaturation enzymes.

There were no important clinical or biochemical side effects during 257 man-months (number of men taking the supplements times the number of months the supplements were consumed) of dietary supplementation with highly purified ethyl esters of EPA or DHA, although transient belching with a taste of fish oil was experienced frequently. Consequently, participants knew they were ingesting an n−3 fatty acid but not whether it was EPA or DHA. This points to a blinding problem in controlled studies with n−3 fatty acids. Compliance was slightly poorer and side effects a little more frequent in the DHA group.

We conclude that both DHA and EPA lower serum triacylglycerol concentration, but have differential effects on lipoprotein and fatty acid metabolism in humans. The present data suggest that effects of individual n−3 fatty acids should be taken into consideration when interpreting the effects of n−3 fatty acid supplementation.

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ATTACHMENT 2a

Details

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The American journal of clinical nutrition.

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v. 2- July/Aug. 1954-

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Diet in disease -- Periodicals

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Available in other form: American journal of clinical nutrition
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Contributor
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450 __ |**a** Diet and disease

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450 __ |**a** Sick |**x** Nutrition

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245 04 The American journal of clinical nutrition : $b AJCN.
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260 New York, N.Y. : $b Journal of Clinical Nutrition, $c [1954]-
260 2 $3 1984- : $a Bethesda, MD : $b American Society for Clinical Nutrition
260 3 $3 2018- : $a Cary, NC : $b Oxford University Press
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310 Monthly, $b <1965-
321 Bimonthly, $b 1954-19
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500 "A publication of the American Society for Nutrition."
510 2 Chemical abstracts $x 0009-2258

525 Supplements accompany some issues.
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588 Latest issue consulted: Vol. 107, no. 2 (Feb. 2018) (surrogate).
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CONTENTS

Adverse Reactions (Excluding Non-Drug Related)	Treatment Group	
	DynaCirc CR® (isradipine) (N=422)	Placebo (N=186)
Edema	15.2%	2.2%
Headache	13.0%	12.4%
Dizziness	4.7%	2.7%
Fatigue	4.3%	2.2%
Abdominal Discomfort	2.8%	0.5%
Flushing	1.9%	0.5%
Constipation	1.7%	0.0%
Palpitations	1.2%	0.0%
Nausea	1.2%	1.6%
Abdominal Distention	1.2%	0.0%

The following adverse experiences were reported in 0.5%–1.0% or less of DynaCirc CR® (isradipine) or immediate-release DynaCirc® (isradipine) treated patients in hypertensive studies, or were noted in postmarketing experience with immediate-release DynaCirc® (isradipine) Capsules. More serious events are shown in italics. The relationship of these adverse experiences to isradipine administration is uncertain.

SKIN: Pruritus, *urticaria, angioedema.*

MUSCULOSKELETAL: backache/pain, joint pain, neck pain/sore/stiff, legs ache/pain, cramps of legs/feet.

RESPIRATORY: Dyspnea, nasal congestion, cough.

CARDIOVASCULAR: Epistaxis, tachycardia, chest pain, shortness of breath, hypotension, *syncope, atrial or ventricular fibrillation, myocardial infarction, heart failure.*

GASTROINTESTINAL: Diarrhea, vomiting, appetite increased or decreased.

UROGENITAL: Pollakiuria, impotence, dysuria, nocturia.

CENTRAL NERVOUS: Drowsiness, insomnia, lethargy, nervousness, libido decrease/frigidity, impotence, depression, *paresthesia* (which includes numbness and tingling), *transient ischemic attack, stroke.*

AUTONOMIC: Dry mouth, hyperhidrosis, visual disturbance.

MISCELLANEOUS: Weight gain, throat discomfort, *drug fever, leukopenia, elevated liver function tests.*

No gastrointestinal bleeding has been reported in clinical trials with DynaCirc CR® (isradipine) Controlled Release Tablets.

In a long-term (one-year) DynaCirc CR® (isradipine) open-label, hypertension trial, the adverse events reported were generally the same as those seen in the short-term placebo-controlled studies. About 6% of DynaCirc CR® (isradipine) treated patients discontinued the long-term trial due to adverse reactions.

With immediate-release DynaCirc® (isradipine) Capsules, most of the adverse experiences were transient, mild, and related to vasodilatory effects. The following table shows the most common adverse events reported in U.S. clinical trials for immediate-release DynaCirc® (isradipine) Capsules, volunteered or elicited, and considered by the investigator to be at least possibly drug related.

[See second table at top of previous page]

In open-label, long-term studies of up to two years in duration with immediate-release DynaCirc® (isradipine) Capsules, the adverse experiences reported were generally the same as those reported in the short-term controlled trials. The overall frequencies of these adverse events were slightly higher in the long-term than in the controlled studies, but in the controlled studies most adverse reactions were mild and transient.

OVERDOSAGE

Although there is no well documented experience with DynaCirc® (isradipine) overdosage, available data suggest that, as with other dihydropyridines, gross overdosage would result in excessive peripheral vasodilation with subsequent marked and probably prolonged systemic hypotension. Clinically significant hypotension overdosage calls for active cardiovascular support including monitoring of cardiac and respiratory function, elevation of lower extremities and attention to circulating fluid volume and urine output. A vasoconstrictor (such as epinephrine, norepinephrine, or levarterenol) may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Since isradipine is highly protein bound, dialysis is not likely to be of benefit.

Significant lethality was observed in mice given oral doses of over 200 mg/kg and rabbits given about 50 mg/kg of isradipine. Rats tolerated doses of over 2000 mg/kg without effects on survival.

DOSAGE AND ADMINISTRATION

The dosage of DynaCirc CR® (isradipine) Controlled Release Tablets should be individualized. The recommended initial dose of DynaCirc CR® (isradipine) is 5 mg once-daily as monotherapy or in combination with a thiazide diuretic. An antihypertensive response usually occurs within 2 hours, with the peak antihypertensive response occurring 8–10 hours post-dose; blood pressure reduction is maintained for at least 24 hours following drug administration. If necessary, the dose may be adjusted in increments of 5 mg at 2–4 week intervals up to a maximum dose of 20 mg/day. Adverse experiences are increased in frequency above 10 mg/day.

DynaCirc CR® (isradipine) Controlled Release Tablets should be swallowed whole and should not be bitten or divided.

The bioavailability (increased AUC) of immediate-release DynaCirc® (isradipine) is increased in elderly patients (above 65 years of age), patients with hepatic functional impairment, and patients with mild renal impairment. Ordinarily, a starting dose of DynaCirc CR® (isradipine) 5 mg once-daily should be used in these patients.

HOW SUPPLIED

DynaCirc CR® (isradipine) Controlled Release Tablets:

5 mg: A light pink, round, standard biconvex and film coated tablet. Printing is in red with "DynaCirc CR" in a semicircle with "5" centered below the semicircle.

Bottles of 30 controlled release tablets (NDC 65726-235-10)

10 mg: A beige, round, standard biconvex and film coated tablet. Printing is in red with "DynaCirc CR" in a semicircle with "10" centered below the semi-circle.

Bottles of 30 controlled release tablets (NDC 65726-236-10)

Store and Dispense:

Below 86°F (30°C) in a tight container, protected from moisture and humidity.

Rx only

Revised: June, 2007

Distributed by:
Reliant Pharmaceuticals, Inc.
Liberty Corner, NJ 07938

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Shown in Product Identification Guide, page 329

LOVAZA™ ℞

[lō-vā-ză]

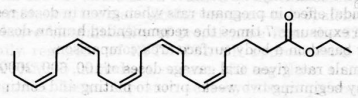
(omega-3-acid ethyl esters)

Capsules

DESCRIPTION

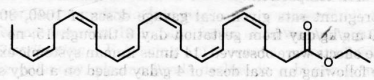
Lovaza, a lipid-regulating agent, is supplied as a liquid-filled gel capsule for oral administration. Each one gram capsule of Lovaza (omega-3-acid ethyl esters) contains at least 900 mg of the ethyl esters of omega-3 fatty acids. These are predominantly a combination of ethyl esters of eicosapentaenoic acid (EPA - approximately 465 mg) and docosahexaenoic acid (DHA - approximately 375 mg).

The structural formula of EPA ethyl ester is:



The empirical formula of EPA ethyl ester is $C_{22}H_{34}O_2$, and the molecular weight of EPA ethyl ester is 330.51.

The structural formula of DHA ethyl ester is:



The empirical formula of DHA ethyl ester is $C_{24}H_{36}O_2$, and the molecular weight of DHA ethyl ester is 356.55.

Lovaza capsules also contain the following inactive ingredients: 4 mg α-tocopherol (in a carrier of partially hydrogenated vegetable oils including soybean oil), and gelatin, glycerol, and purified water (components of the capsule shell).

CLINICAL PHARMACOLOGY

Mechanism of Action:

The mechanism of action of Lovaza is not completely understood. Potential mechanisms of action include inhibition of acyl CoA:1,2-diacylglycerol acyltransferase, increased mitochondrial and peroxisomal β-oxidation in the liver, decreased lipogenisis in the liver, and increased plasma lipoprotein lipase activity. Lovaza may reduce the synthesis of triglycerides (TGs) in the liver because EPA and DHA are poor substrates for the enzymes responsible for TG synthesis, and EPA and DHA inhibit esterification of other fatty acids.

Pharmacokinetic and Bioavailability Studies:

In healthy volunteers and in patients with hypertriglyceridemia (HTG), EPA and DHA were absorbed when administered as ethyl esters orally. Omega-3-acids administered as ethyl esters (Lovaza) induced significant, dose-dependent increases in serum phospholipid EPA content, though increases in DHA content were less marked and not dose-dependent when administered as ethyl esters. Uptake of EPA and DHA into serum phospholipids in subjects treated with Lovaza was independent of age (<49 years vs. ≥49 years). Females tended to have more uptake of EPA into serum phospholipids than males. Pharmacokinetic data on Lovaza in children are not available.

Drug Interactions:

Cytochrome P450-Dependent Monooxygenase Activities:

The effect of a mixture of free fatty acids (FFA), EPA/DHA and their FFA-albumin conjugate on cytochrome P450-dependent monooxygenase activities was assessed in human liver microsomes. At the 23 μM concentration, FFA resulted in a less than 32% inhibition of CYP1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A. At the 23 μM concentration, the FFA-albumin conjugate resulted in a less than 20% inhibition of CYP2A6, 2C19, 2D6, and 3A, with a 68% inhibition being seen for CYP2E1. Since the free forms of the EPA and DHA are undetectable in the circulation (<1 μM), clinically significant drug-drug interactions due to inhibition of P450 mediated metabolism EPA/DHA combinations are not expected in humans.

CLINICAL STUDIES

High Triglycerides: Add-on to HMG-CoA reductase inhibitor therapy

The effects of Lovaza 4 g per day as add-on therapy to treatment with simvastatin were evaluated in a randomized, placebo-controlled, double-blind, parallel-group study of 254 adult patients (122 on Lovaza and 132 on placebo) with persistent high triglycerides (200-499 mg/dL) despite simvastatin therapy (Table 1). Patients were treated with open-label simvastatin 40 mg per day for 8 weeks prior to randomization to control their LDL-C to no greater than 10% above NCEP ATP III goal and remained on this dose throughout the study. Following the 8 weeks of open-label treatment with simvastatin, patients were randomized to either Lovaza 4 g per day or placebo for an additional 8 weeks with simvastatin co-therapy. The median baseline triglyceride and LDL-C levels in these patients were 268 mg/dL and 89 mg/dL, respectively. Median baseline non-HDL-C and HDL-C levels were 138 mg/dL and 45 mg/dL, respectively.

The changes in the major lipoprotein lipid parameters for the Lovaza plus simvastatin and the placebo plus simvastatin groups are shown in Table 1.

[See table 1 below]

Lovaza 4 g per day significantly reduced non-HDL-C, TG, TC, VLDL-C, and Apo-B levels and increased HDL-C and LDL-C from baseline relative to placebo.

Very High Triglycerides: Monotherapy

The effects of Lovaza 4 g per day were assessed in two randomized, placebo-controlled, double-blind, parallel-group studies of 84 adult patients (42 on Lovaza, 42 on placebo) with very high triglyceride levels (Table 2). Patients whose baseline triglyceride levels were between 500 and 2000 mg/dL were enrolled in these two studies of 6 and 16

Continued on next page

Table 1: Response to the Addition of LOVAZA 4 g per day to On-going Simvastatin 40 mg per day Therapy in Patients with High Triglycerides (200 to 499 mg/dL)

Parameter	LOVAZA + Simvastatin N=122			Placebo + Simvastatin N=132			Difference	P-Value
	BL	EOT	Median % Change	BL	EOT	Median % Change		
Non-HDL-C	137	123	-9.0	141	134	-2.2	-6.8	<0.0001
TG	268	182	-29.5	271	260	-6.3	-23.2	<0.0001
TC	184	172	-4.8	184	178	-1.7	-3.1	<0.05
VLDL-C	52	37	-27.5	52	49	-7.2	-20.3	<0.05
Apo-B	86	80	-4.2	87	85	-1.9	-2.3	<0.05
HDL-C	46	48	+3.4	43	44	-1.2	+4.6	<0.05
LDL-C	91	88	+0.7	88	85	-2.8	+3.5	=0.05

BL = Baseline (mg/dL); EOT = End of Treatment (mg/dL); Median % Change = Median Percent Change from Baseline; Difference = LOVAZA Median % Change - Placebo Median % Change

Lovaza—Cont.

weeks duration. The median triglyceride and LDL-C levels in these patients were 792 mg/dL and 100 mg/dL, respectively. Median HDL-C level was 23.0 mg/dL.
The changes in the major lipoprotein lipid parameters for the Lovaza and placebo groups are shown in Table 2.

Table 2: Median Baseline and Percent Change From Baseline in Lipid Parameters in Patients with Very High TG Levels (≥500 mg/dL)

Parameter	LOVAZA N=42		Placebo N=42		Difference
	BL	% Change	BL	% Change	
TG	816	-44.9	788	+6.7	-51.6
Non-HDL-C	271	-13.8	292	-3.6	-10.2
TC	296	-9.7	314	-1.7	-8.0
VLDL-C	175	-41.7	175	-0.9	-40.8
HDL-C	22	+9.1	24	0.0	+9.1
LDL-C	89	+44.5	108	-4.8	+49.3

BL = Baseline (mg/dL); % Chg = Median Percent Change from Baseline; Difference = Lovaza Median % change - Placebo Median % Change

Lovaza 4 g per day reduced median TG, VLDL-C, and non-HDL-C levels and increased median HDL-C from baseline relative to placebo. Lovaza treatment to reduce very high TG levels may result in elevations in LDL-C and non-HDL-C in some individuals. Patients should be monitored to ensure that the LDL-C level does not increase excessively.
The effect of Lovaza on the risk of pancreatitis in patients with very high TG levels has not been evaluated.
The effect of Lovaza on cardiovascular mortality and morbidity in patients with elevated TG levels has not been determined.

INDICATIONS AND USAGE

Very High Triglycerides

Lovaza is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with very high (≥500 mg/dL) triglyceride levels.

Usage Considerations:

In individuals with hypertriglyceridemia (HTG), excess body weight and excess alcohol intake may be important contributing factors and should be addressed before initiating any drug therapy. Physical exercise can be an important ancillary measure. Diseases contributory to hyperlipidemia, (such as hypothyroidism or diabetes mellitus) should be looked for and adequately treated. Estrogen therapy, thiazide diuretics, and beta blockers are sometimes associated with massive rises in plasma TG levels. In such cases, discontinuation of the specific etiologic agent, if medically indicated, may obviate the need for specific drug therapy for HTG.
The use of lipid-regulating agents should be considered only when reasonable attempts have been made to obtain satisfactory results with non-drug methods. If the decision is made to use lipid-regulating agents, the patient should be advised that use of lipid-regulating agents does not reduce the importance of adhering to diet (See PRECAUTIONS).

CONTRAINDICATIONS

Lovaza is contraindicated in patients who exhibit hypersensitivity to any component of this medication.

PRECAUTIONS

General:

Initial Therapy: Laboratory studies should be performed to ascertain that the patient's TG levels are consistently abnormal before instituting Lovaza therapy. Every attempt should be made to control serum TG levels with appropriate diet, exercise, weight loss in overweight patients, and control of any medical problems (such as diabetes mellitus and hypothyroidism) that may be contributing to the patient's TG abnormalities. Medications known to exacerbate HTG (such as beta blockers, thiazides, and estrogens) should be discontinued or changed, if possible, before considering TG-lowering drug therapy.

Continued Therapy: Laboratory studies should be performed periodically to measure the patient's TG levels during Lovaza therapy. Lovaza therapy should be withdrawn in patients who do not have an adequate response after 2 months of treatment.

Information for Patients:

Lovaza should be used with caution in patients with known sensitivity or allergy to fish. Patients should be advised that use of lipid-regulating agents does not reduce the importance of adhering to diet.

Laboratory Tests:

In some patients, increases in alanine aminotransferase (ALT) levels without a concurrent increase in aspartate aminotransferase (AST) levels were observed. Alanine aminotransferase levels should be monitored periodically during Lovaza therapy.
In some patients, Lovaza increased low-density lipoprotein cholesterol (LDL-C) levels. As with any lipid-regulating product, LDL-C levels should be monitored periodically during Lovaza therapy.

Drug Interactions:

Anticoagulants: Some studies with omega-3-acids demonstrated prolongation of bleeding time. The prolongation of bleeding time reported in these studies has not exceeded normal limits and did not produce clinically significant bleeding episodes. Clinical studies have not been done to thoroughly examine the effect of Lovaza and concomitant anticoagulants. Patients receiving treatment with both Lovaza and anticoagulants should be monitored periodically.

HMG-CoA reductase inhibitors: In a 14-day study of 24 healthy adult subjects, daily co-administration of simvastatin 80 mg with Lovaza 4 g did not affect the extent (AUC) or rate (C_{max}) of exposure to simvastatin or the major active metabolite, beta-hydroxy simvastatin at steady state.

Cytochrome P450-Dependent Monooxygenase Activities: Omega-3-fatty acid containing products have been shown to increase hepatic concentrations of cytochrome P450 and activities of certain P450 enzymes in rats. The potential of Lovaza to induce P450 activities in humans has not been studied.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

In a rat carcinogenicity study with oral gavage doses of 100, 600, 2000 mg/kg/day by oral gavage, males were treated with omega-3-acid ethyl esters for 101 weeks and females for 89 weeks without an increased incidence of tumors (up to 5 times human systemic exposures following an oral dose of 4 g/day based on a body surface area comparison). Standard lifetime carcinogenicity bioassays were not conducted in mice.
Omega-3-acid ethyl esters were not mutagenic or clastogenic with or without metabolic activation in the bacterial mutagenesis (Ames) test with *Salmonella typhimurium* and *Escherichia coli* or in the chromosomal aberration assay in Chinese hamster V79 lung cells or human lymphocytes. Omega-3-acid ethyl esters were negative in the *in vivo* mouse micronucleus assay.
In a rat fertility study with oral gavage doses of 100, 600, 2000 mg/kg/day, males were treated for 10 weeks prior to mating and females were treated for 2 weeks prior to and throughout mating, gestation and lactation. No adverse effect on fertility was observed at 2000 mg/kg/day (5 times human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison).

Pregnancy Category C:

There are no adequate and well-controlled studies in pregnant women. It is unknown whether Lovaza can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Lovaza should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Omega-3-acid ethyl esters have been shown to have an embryocidal effect in pregnant rats when given in doses resulting in exposures 7 times the recommended human dose of 4 g/day based on a body surface area comparison.
In female rats given oral gavage doses of 100, 600, 2000 mg/kg/day beginning two weeks prior to mating and continuing through gestation and lactation, no adverse effects were observed in the high dose group (5 times human systemic exposure following an oral dose of 4 g/day based on body surface area comparison).
In pregnant rats given oral gavage doses of 1000, 3000, 6000 mg/kg/day from gestation day 6 through 15, no adverse effects were observed (14 times human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison).
In pregnant rats given oral gavage doses of 100, 600, 2000 mg/kg/day from gestation day 14 through lactation day 21, no adverse effects were seen at 2000 mg/kg/day (5 times the human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison). However, decreased live births (20% reduction) and decreased survival to postnatal day 4 (40% reduction) were observed in a dose-ranging study using higher doses of 3000 mg/kg/day (7 times the human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison).
In pregnant rabbits given oral gavage doses of 375, 750, 1500 mg/kg/day from gestation day 7 through 19, no findings were observed in the fetuses in groups given 375 mg/kg/day (2 times human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison). However, at higher doses, evidence of maternal toxicity was observed (4 times human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison).

Nursing Mothers:

It is not known whether omega-3-acid ethyl esters are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Lovaza is administered to a woman who is breastfeeding.

Pediatric Use:

Safety and effectiveness in pediatric patients under 18 years of age have not been established.

Geriatric Use:

A limited number of patients over 65 years of age were enrolled in the clinical studies. Safety and efficacy findings in subjects over 60 years of age did not appear to differ from those of subjects less than 60 years of age.

ADVERSE REACTIONS

Treatment-emergent adverse events reported in at least 1% of patients treated with Lovaza 4 g per day or placebo during 8 randomized, placebo-controlled, double-blind, parallel-group studies for HTG are listed in Table 3. Adverse events led to discontinuation of treatment in 3.5% of patients treated with Lovaza and 2.6% of patients treated with placebo.

Table 3: Adverse Events in Randomized, Placebo-Controlled, Double-Blind, Parallel-Group Studies for Very High TG Levels (≥ 500 mg/dL) that Used LOVAZA 4 g per Day

BODY SYSTEM Adverse Event	LOVAZA (N = 226) n	%	Placebo* (N = 228) n	%
Subjects with at least 1 adverse event	80	35.4	63	27.6
Body as a whole				
Back pain	5	2.2	3	1.3
Flu syndrome	8	3.5	3	1.3
Infection	10	4.4	5	2.2
Pain	4	1.8	3	1.3
Cardiovascular				
Angina pectoris	3	1.3	2	0.9
Digestive				
Dyspepsia	7	3.1	6	2.6
Eructation	11	4.9	5	2.2
Skin				
Rash	4	1.8	1	0.4
Special senses				
Taste perversion	6	2.7	0	0.0

Adverse events were coded using COSTART, version 5.0. Subjects were counted only once for each body system and for each preferred term.
*Placebo was corn oil for all studies.

Additional adverse events reported by 1 or more patients from 22 clinical studies for HTG are listed below:
BODY AS A WHOLE: Enlarged abdomen, asthenia, body odor, chest pain, chills, suicide, fever, generalized edema, fungal infection, malaise, neck pain, neoplasm, rheumatoid arthritis, and sudden death.
CARDIOVASCULAR SYSTEM: Arrhythmia, bypass surgery, cardiac arrest, hyperlipemia, hypertension, migraine, myocardial infarct, myocardial ischemia, occlusion, peripheral vascular disorder, syncope, and tachycardia.
DIGESTIVE SYSTEM: Anorexia, constipation, dry mouth, dysphagia, colitis, fecal incontinence, gastritis, gastroenteritis, gastrointestinal disorder, increased appetite, intestinal obstruction, melena, pancreatitis, tenesmus, and vomiting.
HEMATOLOGIC-LYMPHATIC SYSTEM: Lymphadenopathy.
INFECTIONS AND INFESTATIONS: Viral infection.
METABOLIC AND NUTRITIONAL DISORDERS: Edema, hyperglycemia, increased ALT, and increased AST.
MUSCULOSKELETAL SYSTEM: Arthralgia, arthritis, myalgia, pathological fracture, and tendon disorder.
NERVOUS SYSTEM: Central nervous system neoplasia, depression, dizziness, emotional lability, facial paralysis, insomnia, vasodilatation, and vertigo.
RESPIRATORY SYSTEM: Asthma, bronchitis, increased cough, dyspnea, epistaxis, laryngitis, pharyngitis, pneumonia, rhinitis, and sinusitis.
SKIN: Alopecia, eczema, pruritus, and sweating.
SPECIAL SENSES: Cataract.
UROGENITAL SYSTEM: Cervix disorder, endometrial carcinoma, epididymitis, and impotence.

DRUG ABUSE AND DEPENDENCE

Lovaza does not have any known drug abuse or withdrawal effects.

OVERDOSAGE

In the event of an overdose, the patient should be treated symptomatically, and general supportive care measures instituted, as required.

DOSAGE AND ADMINISTRATION

Patients should be placed on an appropriate lipid-lowering diet before receiving Lovaza, and should continue this diet during treatment with Lovaza. In clinical studies, Lovaza was administered with meals.
The daily dose of Lovaza is 4 g per day. The daily dose may be taken as a single 4-g dose (4 capsules) or as two 2-g doses (2 capsules given twice daily).

HOW SUPPLIED

Lovaza (omega-3-acid ethyl esters) capsules are supplied as 1-gram transparent soft-gelatin capsules filled with light-yellow oil and bearing the designation REL900 in bottles of 60 (NDC 65726-425-15) and 120 (NDC 65726-425-27).

Recommended Storage:

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. Do not freeze. Keep out of reach of children.

Rx only

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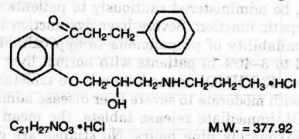
Shown in Product Identification Guide, page 329

RYTHMOL® SR Rx

[ryth-mul]
(propafenone hydrochloride) extended release CAPSULES

DESCRIPTION

RYTHMOL SR (propafenone hydrochloride) is an antiarrhythmic drug supplied in extended-release capsules of 225, 325 and 425 mg for oral administration.
The structural formula of propafenone HCl is given below:



$C_{21}H_{27}NO_3$ •HCl M.W. = 377.92

2'-[2-Hydroxy-3-(propylamino) -propoxy]-3-phenylpropiophenone hydrochloride

Propafenone HCl has some structural similarities to beta-blocking agents. Propafenone HCl occurs as colorless crystals or white crystalline powder with a very bitter taste. It is slightly soluble in water (20°C), chloroform and ethanol. Rythmol SR are capsules filled with cylindrical-shaped 2 × 2 mm microtablets containing propafenone and the following inactive ingredients: antifoam, gelatin, hypromellose, red iron oxide, magnesium stearate, shellac, sodium lauryl sulfate, sodium dodecyl sulfate, soy lecithin and titanium dioxide.

CLINICAL PHARMACOLOGY

Mechanism of Action:
Propafenone is a Class 1C antiarrhythmic drug with local anesthetic effects, and a direct stabilizing action on myocardial membranes. The electrophysiological effect of propafenone manifests itself in a reduction of upstroke velocity (Phase 0) of the monophasic action potential. In Purkinje fibers, and to a lesser extent myocardial fibers, propafenone reduces the fast inward current carried by sodium ions. Diastolic excitability threshold is increased and effective refractory period prolonged. Propafenone reduces spontaneous automaticity and depresses triggered activity. Studies in anesthetized dogs and isolated organ preparations show that propafenone has beta-sympatholytic activity at about 1/50 the potency of propranolol. Clinical studies employing isoproterenol challenge and exercise testing after single doses of propafenone indicate a beta-adrenergic blocking potency (per mg) about 1/40 that of propranolol in man. In clinical trials with the immediate release formulation, resting heart rate decreases of about 8% were noted at the higher end of the therapeutic plasma concentration range. At very high concentrations *in vitro*, propafenone can inhibit the slow inward current carried by calcium, but this calcium antagonist effect probably does not contribute to antiarrhythmic efficacy. Moreover, propafenone inhibits a variety of cardiac potassium currents in *in vitro* studies (i.e. the transient outward, the delayed rectifier, and the inward rectifier current). Propafenone has local anesthetic activity approximately equal to procaine. Compared to propafenone, the main metabolite, 5-hydroxypropafenone, has similar sodium and calcium channel activity, but about 10 times less beta-blocking activity (N-depropylpropafenone has weaker sodium channel activity but equivalent affinity for beta-receptors).

Electrophysiology:
Electrophysiology studies in patients with ventricular tachycardia (VT) have shown that propafenone prolongs atrioventricular (AV) conduction while having little or no effect on sinus node function. Both atrioventricular (AV) nodal conduction time (AH interval) and His-Purkinje conduction time (HV interval) are prolonged. Propafenone has little or no effect on the atrial functional refractory period, but AV nodal functional and effective refractory periods are prolonged. In patients with Wolff-Parkinson-White (WPW) syndrome, RYTHMOL immediate release tablets reduce conduction and increase the effective refractory period of the accessory pathway in both directions (see **ADVERSE REACTIONS/Electrocardiograms**).

Hemodynamics:
Studies in humans have shown that propafenone exerts a negative inotropic effect on the myocardium. Cardiac catheterization studies in patients with moderately impaired ventricular function (mean C.I. = 2.61 L/min/m^2), utilizing intravenous propafenone infusions (loading dose of 2 mg/kg over 10 min+ followed by 2 mg/min for 30 min) that gave mean plasma concentrations of 3.0 µg/mL (a dose that produces plasma levels of propafenone greater than does recommended oral dosing), showed significant increases in pulmonary capillary wedge pressure, systemic and pulmonary vascular resistances and depression of cardiac output and cardiac index.

Table 1: Analysis of tachycardia-free period (days) from Day 1 of randomization

Parameter	RYTHMOL SR Dose 225 mg BID (N = 126) n (%)	325 mg BID (N = 135) n (%)	425 mg BID (N = 136) n (%)	Placebo (N = 126) n (%)
Patients completing with terminating event†	66 (52)	56 (41)	41 (30)	87 (69)
Comparison of tachycardia-free periods				
Kaplan-Meier Median	112	291	*	41
Range	0 – 285	0 – 293	0 – 300	0 – 289
p-Value (Log-rank test)	0.014	< 0.0001	< 0.0001	—
Hazard Ratio compared to placebo	0.67	0.43	0.35	—
95% CI for Hazard Ratio	(0.49, 0.93)	(0.31, 0.61)	(0.24, 0.51)	—

* Fewer than 50% of the patients had events. The median time is not calculable.
† Terminating events comprised 91% atrial fibrillation, 5% atrial flutter, and 4% PSVT.

Pharmacokinetics and Metabolism:
Absorption/Bioavailability: Maximal plasma levels of propafenone are reached between three to eight hours following the administration of RYTHMOL SR. Propafenone is known to undergo extensive and saturable presystemic biotransformation which results in a dose and dosage form dependent absolute bioavailability; e.g., a 150 mg immediate release tablet had an absolute bioavailability of 3.4%, while a 300 mg immediate release tablet had an absolute bioavailability of 10.6%. Absorption from a 300 mg solution dose was rapid, with an absolute bioavailability of 21.4%. At still larger doses, above those recommended, bioavailability of propafenone from immediate release tablets increased still further.
Relative bioavailability assessments have been performed between RYTHMOL SR capsules and RYTHMOL immediate release tablets. In extensive metabolizers, the bioavailability of propafenone from the SR formulation was less than that of the immediate release formulation as the more gradual release of propafenone from the prolonged-release preparations resulted in an increase in overall first pass metabolism (see **Metabolism**). As a result of the increased first pass effect, higher daily doses of propafenone were required from the SR formulation relative to the immediate release formulation, to obtain similar exposure to propafenone. The relative bioavailability of propafenone from the 325 twice daily regimens of RYTHMOL SR approximates that of RYTHMOL immediate release 150 mg three times daily regimen. Mean exposure to 5-hydroxypropafenone was about 20–25% higher after SR capsule administration than after immediate-release tablet administration.
Food increased the exposure to propafenone 4-fold after single dose administration of 425 mg of RYTHMOL SR. However, in the multiple dose study (425 mg dose BID), the difference between the fed and fasted state was not significant.
Distribution: Following intravenous administration of propafenone, plasma levels decline in a bi-phasic manner consistent with a two compartment pharmacokinetic model. The average distribution half-life corresponding to the first phase was about five minutes. The volume of the central compartment was about 88 liters (1.1 L/kg) and the total volume of about 252 liters.
In serum, propafenone is greater than 95% bound to proteins within the concentration range of 0.5 – 2 µg/mL. Protein binding decreases to about 88% in patients with severe hepatic dysfunction.
Metabolism: There are two genetically determined patterns of propafenone metabolism. In over 90% of patients, the drug is rapidly and extensively metabolized with an elimination half-life from 2–10 hours. These patients metabolize propafenone into two active metabolites: 5-hydroxypropafenone which is formed by CYP2D6 and N-depropylpropafenone (norpropafenone) which is formed by both CYP3A4 and CYP1A2. In less than 10% of patients, metabolism of propafenone is slower because the 5-hydroxy metabolite is not formed or is minimally formed. In these patients, the estimated propafenone elimination half-life ranges from 10–32 hours. Decreased ability to form the 5-hydroxy metabolite of propafenone is associated with a diminished ability to metabolize debrisoquine and a variety of other drugs such as encainide, metoprolol, and dextromethorphan whose metabolism is mediated by the CYP2D6 isozyme. In these patients, the N-depropylpropafenone metabolite occurs in quantities comparable to the levels occurring in extensive metabolizers.
As a consequence of the observed differences in metabolism, administration of RYTHMOL SR to slow and extensive metabolizers results in significant differences in plasma concentrations of propafenone, with slow metabolizers achieving concentrations about twice those of the extensive metabolizers at daily doses of 850 mg/day. At low doses the differences are greater, with slow metabolizers attaining concentrations about three to four times higher than extensive metabolizers. In extensive metabolizers, saturation of the hydroxylation pathway (CYP2D6) results in greater-than-linear increases in plasma levels following administration of RYTHMOL SR capsules. In slow metabolizers, propafenone pharmacokinetics are linear. Because the difference decreases at high doses and is mitigated by the lack of the active 5-hydroxy metabolite in the slow metabolizers, and because steady-state conditions are achieved after four to five days of dosing in all patients, the recommended dosing regimen of RYTHMOL SR is the same for all patients. The large inter-subject variability in blood levels require that the dose of the drug be titrated carefully in patients with close attention paid to clinical and ECG evidence of toxicity (see **DOSAGE AND ADMINISTRATION**).
The 5-hydroxypropafenone and norpropafenone metabolites have electrophysiologic properties similar to propafenone *in vitro*. In man after administration of RYTHMOL SR, the 5-hydroxypropafenone metabolite is usually present in concentrations less than 40% of propafenone. The norpropafenone metabolite is usually present in concentrations less than 10% of propafenone.
Inter-Subject Variability:
With propafenone, there is a considerable degree of inter-subject variability in pharmacokinetics which is due in large part to the first pass hepatic effect and non-linear pharmacokinetics in extensive metabolizers. A higher degree of inter-subject variability in pharmacokinetic parameters of propafenone was observed following both single and multiple dose administration of RYTHMOL SR capsules. Inter-subject variability appears to be substantially less in the poor metabolizer group than in the extensive metabolizer group, suggesting that a large portion of the variability is intrinsic to CYP2D6 polymorphism rather than to the formulation.
The clearance of propafenone is reduced and the elimination half-life increased in patients with significant hepatic dysfunction (see **PRECAUTIONS**). Decreased liver function also increases the bioavailability of propafenone. Absolute bioavailability assessments have not been determined for the RYTHMOL SR capsule formulation. Absolute bioavailability of RYTHMOL immediate release tablets has been demonstrated to be inversely related to indocyanine green clearance, reaching 60–70% at clearances of 7 mL/min and below.
Stereochemistry:
RYTHMOL is a racemic mixture. The R- and S-enantiomers of propafenone display stereoselective disposition characteristics. *in vitro* and *in vivo* studies have shown that the R-isomer of propafenone is cleared faster than the S-isomer via the 5-hydroxylation pathway (CYP2D6). This results in a higher ratio of S-propafenone to R-propafenone at steady state. Both enantiomers have equivalent potency to block sodium channels; however, the S-enantiomer is a more potent ß-antagonist than the R-enantiomer. Following administration of RYTHMOL immediate release tablets or RYTHMOL SR capsules, the S/R ratio for the area under the plasma concentration-time curve was about 1.7. The S/R ratios of propafenone obtained after administration of 225, 325 and 425 mg RYTHMOL SR are independent of dose. In addition, no difference in the average values of the S/R ratios is evident between genotypes or over time.
Clinical Trials:
RYTHMOL SR has been evaluated in patients with a history of electrocardiographically documented recurrent episodes of symptomatic atrial fibrillation in two randomized, double-blind, placebo controlled trials.
RAFT: In one US multicenter study (Rythmol SR Atrial Fibrillation Trial, RAFT), three doses of RYTHMOL SR (225 mg BID, 325 mg BID and 425 mg BID) and placebo were compared in 523 patients with symptomatic, episodic atrial fibrillation. The patient population in this trial was 59% male with a mean age of 63 years, 91% White and 6% Black. The patients had a median history of atrial fibrillation of 13 months, and documented symptomatic atrial fi-

Continued on next page