Epilepsy & Behavior 13 (2008) 681–684

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

n-3 Fatty acids (fish oil) for epilepsy, cardiac risk factors, and risk of SUDEP: Clues from a pilot, double-blind, exploratory study ☆

Christopher M. DeGiorgio [a,*], Patrick Miller [a], Sheba Meymandi [b], Jeffrey A. Gornbein [c]

[a] Department of Neurology, David Geffen School of Medicine at UCLA, Los Angeles, CA 90095, USA
[b] Department of Cardiology, David Geffen School of Medicine at UCLA, Los Angeles, CA 90095, USA
[c] Department of Biomathematics, David Geffen School of Medicine at UCLA, Los Angeles, CA 90095, USA

ARTICLE INFO

Article history:
Received 2 July 2008
Revised 29 July 2008
Accepted 1 August 2008
Available online 7 September 2008

Keywords:
n-3 Fatty acids
PUFA
EPA
DHA
Epilepsy
Seizures
Heart rate variabiity
SUDEP
Sudden death

ABSTRACT

Objective: The goal of the work described here was to determine the effect of high-dose *n*-3 fatty acids (eicosapentanoic acid + docosahexanoic acid, fish oil) on several outcomes in subjects with refractory epilepsy, including seizure severity, seizure frequency, cardiac risk factors, and heart rate variability, in a pilot, exploratory planning trial.

Methods: Pilot, randomized, double-blind two-period crossover clinical trial of high-dose fish oil (9600 mg of fish oil/day, 2880 mg of *n*-3 fatty acids) in 11 subjects with refractory seizures. Outcomes included seizure frequency, seizure severity, lipid panel, and heart rate variability as measured by SDNN and SDANN (defined as the standard deviation of all normal R–R intervals for 1 h, and the standard deviation of all R–R intervals in each successive 5-min epoch, respectively).

Results: Preliminary data identified trends towards lower seizure severity, lower triglycerides, higher HDL, and increased SDNN/SDANN in those with low SDNN/SDANN at baseline (Spearman's correlation = −0.65, $P = 0.03$). No positive effect on seizure frequency was identified.

Conclusions: Further study of the effect of *n*-3 fatty acids is indicated in people with epilepsy, as favorable trends were identified on cardiac risk factors (triglycerides) and in a subgroup with low heart rate variability (low SDNN/SDANN), a marker of sudden death risk. To our knowledge, this is the first trial to explore the beneficial effects of *n*-3 fatty acids on cardiac risk factors and heart rate variability in people with epilepsy.

1. Introduction

Sudden unexpected death in epilepsy (SUDEP) is a major cause of death in epilepsy, and accounts for up to 20% of mortality [1–5]. SUDEP is 24 times more common than sudden death in age-matched controls, and tends to occur in young people, especially 20- to 40-year-olds [1–5]. In the population with medically intractable seizures, SUDEP is up to five times more common than in people with well-controlled epilepsy [1]. Key risk factors are low IQ, generalized tonic–clonic seizures, and polytherapy with antiepileptic drugs [1]. Likely causes of sudden death include seizure-induced cardiac arrhythmias caused by impaired autonomic regulation and respiratory disturbance related to asphyxia or central/obstructive apnea [4–10]. Heart rate variability (HRV), a measure of autonomic regulation, is an important marker for the risk for sudden death in people with heart disease [11,12]. After myocardial infarction, there is a significant decrease in HRV, which is associated with increased mortality [11,12]. This decrease in HRV causes electrical instability of the myocardium, which may provoke arrhythmias [11,12]. Like heart disease, epilepsy is also associated with abnormally reduced HRV [7–10]. Interestingly, *n*-3 fatty acids (eicosapentanoic acid [EPA] and docosahexanoic acid [DHA] as fish oil) improve HRV in patients with heart disease, reduce lethal arrhythmias, and reduce the risk of sudden death [11–16]. In preparation for a larger National Institutes of Health (NIH)/National Center for Complementary and Alternative Medicine (NCCAM)-sponsored clinical trial, we explored the hypothesis that *n*-3 fatty acids may improve cardiac risk factors and HRV in people with intractable epilepsy.

2. Methods

Eleven subjects with intractable epilepsy were enrolled in an exploratory randomized, double-blind, two-period crossover trial of *n*-3 fatty acids (EPA + DHA as fish oil). Fish oil capsules and soybean oil placebo were provided by Pharmavite, Inc, Valencia, CA, USA. Subjects were randomized to eight capsules/day of high-dose

☆ Supported by NIH Grant M01-RR00865, and grants from Mr. James Peters, the Salter Family Trust, and the Lagermeier, Brill, and Lester families (AMDG).
* Corresponding author. Fax: +1 310 794 7491.
E-mail address: cmd@mednet.ucla.edu (C.M. DeGiorgio).

1525-5050/$ - see front matter © 2008 Elsevier Inc. All rights reserved.
doi:10.1016/j.yebeh.2008.08.001

fish oil for 12 weeks or eight capsules/day of soybean oil placebo. Subjects then entered a 6-week washout period during which no study drug was taken, and then they were crossed over to the other treatment. During each treatment period, subjects were administered eight 1200-mg fish oil capsules (216 mg EPA + 144 mg DHA), for a total of 2880 mg of *n*-3 fatty acids/day, or eight soybean oil placebo capsules per day, matched for color, odor, and taste. A certificate of analysis is on file.

The crossover protocol is summarized in Fig. 1.

The UCLA Office for the Protection of Human Subjects approved the protocol. Inclusion criteria were male or female, age 18–65, and a history of intractable localization-related/partial onset seizures and generalized tonic–clonic or tonic seizures defined according to International League Against Epilepsy (ILAE) classification as: a history compatible with localization-related partial epilepsy; a history of generalized tonic–clonic or tonic seizures with loss of consciousness; three or more simple partial, complex partial, or tonic–clonic seizures per month; evidence of at least three seizures per month for at least 2 months prior to the study; exposure to at least one antiepileptic drug at an adequate dose.

Exclusion criteria were significant or progressive medical, cardiac, or other illness; allergy to fish products or fish oil; history of a coagulation disorder; history of nonepileptic seizures; pregnancy; consumption of fish oil at any time 30 days or less prior to enrollment; any change in antiepileptic drugs for 30 days or less prior to enrollment; daily consumption of aspirin (subjects who took aspirin 81–325 mg no more frequently than every other day were allowed) or treatment with warfarin for 30 days or less prior to enrollment; previous poor compliance with therapy; drug or alcohol abuse; uncountable seizures as a result of seizure clustering; and inadequate supervision if the patient was not able count his or her own seizures.

Outcomes measured were seizure frequency, seizure severity, SDNN and SDANN (defined as the standard deviation of all normal R–R intervals for 1 h and the standard deviation of all R–R intervals in each successive 5-min epoch, respectively, expressed in milliseconds [17]), high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, heart rate (HR), cholesterol, and mean arterial pressure (MAP).

One-hour ambulatory ECG monitoring (Holter monitoring) was performed at the screening visit and at the last visit of each treatment period. During all 1-h sessions, subjects sat quietly in a chair or upright in bed while awake. Recordings were performed using a Philips Zymed digital three-channel Holter recording system, recording at a sampling rate of 175 Hz, bandpass 0.5–60 Hz. Heart rate variability was determined using accepted standards [17].

2.1. Statistical analysis

Mean comparisons of the change from baseline for all continuous outcomes were made using a repeated-measure model for a crossover design controlling for the potential effects of period and differential treatment (order). Means ± SE are reported unless otherwise indicated. Mean change from baseline and its SE is reported as a percentage of the baseline mean as an aid in interpretation. Association between continuous baseline variables and the corresponding continuous treatment minus baseline changes were assessed via Pearson and Spearman correlation coefficients.

3. Results

Table 1 summarizes the results. Seizure severity, as measured by the National Hospital Seizure Severity Scale, was reduced from a median score of 8 at baseline, to 7 during the fish oil period and 7 for the soybean oil placebo period [18]. The mean seizure severity scale was reduced from 8.55 at baseline to 7.57 for fish oil and to 7.00 for soybean oil placebo, but these differences were not significant. There was no positive effect of fish oil on seizure frequency: seizure frequency was increased 11% with fish oil versus 14% with soybean oil placebo ($P = 0.051$ for both fish oil and placebo). As for cardiac risk factors, the median HDL increased from a baseline level of 52 mg/dl to 56 mg/dl during the soybean oil placebo period and to 60 mg/dl during the fish oil period, a 7.6% increase in HDL for the fish oil treatment period. The mean HDL was modestly increased, but this was not significant ($P = 0.7996$) (see Table 1). The median triglyceride level was reduced from 91 mg/dl during baseline to 90 mg/dl for the soybean oil placebo period and 68 mg/dl for the fish oil period. The mean triglyceride level was reduced from 117.18 mg/dl at baseline to 76 mg/dl during the fish oil period and to 100.70 for the soybean oil period, but because of the sample size, this difference was not significant ($P = 0.4453$). Although not statistically significant, the mean effect on triglycerides was doubled for fish oil compared with soybean oil (36% vs 17%). The effects of fish oil on other cardiac risk factors were negligible (see Table 1).

As for Heart Rate Variability, fish oil did not increase HRV (SDNN) for the group as a whole. However, of the five subjects with very low HRV, defined as an SDNN <50, 3/5 subjects had an increase in SDNN. In this subgroup of subjects with very low HRV, the mean SDNN increased from a baseline mean of 38.8 ms to 46.6 ms during fish oil ($P = 0.31$). This result is in contrast to a mean 4.9-ms *decrease* in SDNN during soybean oil treatment. In the same subgroup, SDANN improved in 4/5 subjects, and the SDANN increased from 17.1 to 21.2 ms ($P = 0.098$) during fish oil. Response to fish oil was inversely correlated with SDNN; that is, fish oil tended to improve HRV in those at highest risk (i.e., those with the lowest baseline. SDNN/SDANN, Spearman's correlation = −0.65, $P = 0.03$). There was no corresponding correlation during soybean oil placebo treatment (Spearman's correlation = 0.15, $P = 0.67$) (see Fig. 2).

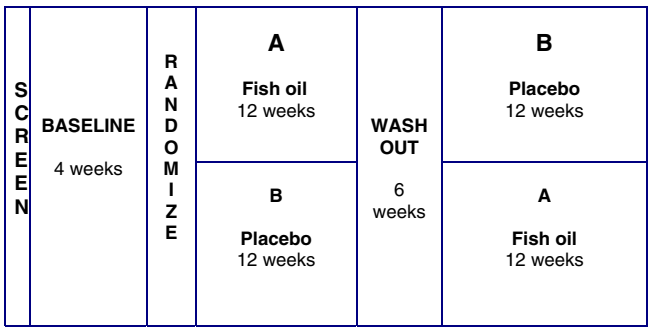

Fig. 1. Crossover protocol.

Table 1
Mean percentage change from baseline due to fish oil versus soybean oil placebo

Outcome	Baseline	Fish oil	Soybean oil placebo	*P* value
Seizures/day	0.61	+11 ± 13%	+14 ± 13%	0.051
Seizure severity	8.55	−12 ± 9%	−19 ± 9%	0.6189
HDL (mg/dl)	59.5	+5 ± 5%	+7 ± 5%	0.7996
Triglycerides (mg/dl)	124.3	−36 ± 17%	−17 ± 17%	0.4453
SDNN (ms)	61.4	−11 ± 10%	−4 ± 10%	0.5891
SDANN (ms)	37.1	−28 ± 18%	−4 ± 18%	0.3711
Heart rate (HR)	72.2	+3 ± 3%	+2 ± 3%	0.8513
Cholesterol (mg/dl)	181.7	−2 ± 5%	−3 ± 5%	0.8999
LDL (mg/dl)	97.3	+3 ± 6%	−4 ± 6%	0.4325
MAP (mm Hg)	91.1	+2 ± 3%	+2 ± 3%	0.8864

Note. Values are means ± SE over both periods.