A Double-Blind, Placebo-Controlled Trial of Fish Oil Concentrate (MaxEpa) in Stroke Patients

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SUMMARY The feeding of large amounts of fish or fish oils to healthy volunteers has been shown to reduce plasma triglycerides and platelet aggregation, and prolong the skin bleeding time. To determine whether a commercially available marine oil (MaxEpa) would have similar effect in stroke patients, we performed a double-blind, placebo-controlled study in 11 patients (7 men, 4 women) with completed stroke (7) or transient ischemic attacks (TIA's) (4). Ten 1 ml opaque capsules containing either MaxEpa or olive oil were given daily for 6 weeks, and then the patients were crossed-over. Aspirin was avoided during the trial. The data were analyzed by paired-sample t-tests.

A significant reduction was found in serum triglycerides, but total serum cholesterol and HDL cholesterol were unaffected. The bleeding time was modestly prolonged after 3 weeks of treatment, but the differences between MaxEpa and olive oil treatments were not significant at 6 weeks. Aside from an increase in collagen-stimulated malondialdehyde formation no other statistically significant changes in hemostatic factors were observed. We conclude that the ingestion of up to 10 MaxEpa capsules daily for 6 weeks has little influence on such established risk factors as cholesterol concentration and platelet function in patients with stroke or TIA's.

STUDIES ORIGINALLY conducted by Dyerberg and Bang1 have focused attention on the link between habitual ingestion of fatty acids of marine origin and the low death rates from atherosclerotic disease in Eskimos. Recently, Goodnight et al2 summarized the results of studies involving the feeding of fish oil supplements to animals and humans. These revealed that fish oils are at least as hypcholesterolemic as polyunsaturated vegetable oils. Furthermore, the reductions in triglycerides and VLDL cholesterol are greater with fish than with vegetable oils. Most importantly, levels of HDL cholesterol were unchanged, resulting in greater HDL:LDL ratios.

In addition to these effects on plasma lipids, chronic feeding of fish oils has been reported to cause a reduction in platelet function.3-7 The effects on bleeding time and platelet aggregation were found to be equivalent to or greater than those produced by aspirin. Furthermore, since there is some evidence that prostacyclin-like function may be retained during fish oil feeding,8 and the balance between prostacyclin and thromboxane shifted in favor of the former, fish oils would be preferred to aspirin, which inhibits both prostacyclin and thromboxane synthesis. Additional advantages of fish oils include their ability to reduce plasma lipids and possibly blood pressure,1 and they do not cause gastritis as does aspirin.

MaxEpa is a commercially available nutritional supplement prepared from refined fish oil. Early studies indicate that MaxEpa can increase the skin bleeding time and inhibit platelet aggregation9-10. In view of these actions, we decided to administer this product to patients with well-defined atherosclerotic disease, using a double-blind placebo-controlled protocol and recording effects on cholesterol, triglycerides, and platelet function.

Methods

Patients and Study Plan

Patients were derived from two sources: inpatients at the Rehabilitation Institute of Chicago, and outpatients of two consulting neurologists. In each case, the diagnosis of occlusive cerebrovascular disease was confirmed by clinical examination, computed tomography, and angiography. When initially examined, most patients were taking aspirin and dipyridamole. The former was discontinued, but the latter was permitted. Patients remained on the diets prescribed by their attending physicians, and no changes in diet or medications occurred during the course of the study. A table of random numbers was kept by the pharmacy, and as patients were entered into the study, the pharmacists dispensed either study medication or placebo based on this table. The medications were packaged in opaque capsules; the study medicine was MaxEpa (Seven Seas Health Care Limited, Hull, U.K.), a fish lipid concentrate containing 180 mg of eicosapentaenoic acid (EPA) per capsule, and the placebo was olive oil. Vitamin E, 100 mg per 100 g, was added to each oil to prevent oxidation. Ten capsules were given daily in divided doses; after 6 weeks, the subjects were switched from olive oil to MaxEpa or vice-versa. At baseline and at 3 week intervals during the course of the study, the patients were questioned about new or continuing symptoms, and laboratory studies were performed. Informed consent was obtained from all subjects in accordance with the Institutional Review Board guidelines of Northwestern University.

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Laboratory Methods

Bleeding times were performed according to Mielke et al. Using the Simplate II device (General Diagnostics, Morris Plains), platelet aggregation was assessed with collagen, adenosine diphosphate (Sigma, St. Louis) and arachidonate (Nuchek Prep, Minn) used at threshold concentrations, as determined for each individual patient. The changes in light transmission 2 min after the addition of the aggregating agent was recorded. Platelet malondialdehyde formation in response to collagen and arachidonate was measured as described by Smith et al. and McMillan et al. Factor VIII-related antigen was quantitated by electroimmunoassay. Total cholesterol, triglycerides, and high density lipoprotein (HDL) cholesterol were measured after overnight fasting. The data were analyzed using paired t-tests, comparing the values obtained after 3 and 6 weeks of olive oil administration to those observed following 3 and 6 weeks of MaxEpa treatment.

Results

Eighteen patients were initially enrolled into the study, but 7 failed to complete the trial. Of these, 4 with completed strokes were unable to swallow the requisite number of capsules, 2 developed acute, non-vascular illnesses necessitating discontinuance of the study medication, and one failed to return after 3 visits. The baseline characteristics of the 11 patients who completed the trial are shown in Table 1. There were 7 men and 4 women; 6 had completed strokes and one had an asymptomatic occlusion of his right carotid artery. Four subjects had TIA's, including two with visual signs, one with episodes of global amnesia, and another with dizziness and vertigo. Three patients had increased levels of both total cholesterol and triglycerides; 4 patients had a reduction in HDL-cholesterol. Factor VIII related antigen levels were elevated in 8 of the 11 patients (73%).

Seven subjects were randomized to receive olive oil as their initial treatment, and 4 were given MaxEpa first. Both the olive oil and the MaxEpa were well-tolerated, and there were no complaints such as epigastric distress, nausea, diarrhea, or headache. Symptoms of transient cerebral ischemia persisted in two of the 4 patients (subjects 3 and 4) during the phase of the trial in which they were receiving MaxEpa as well as during the olive oil period. The results of the laboratory evaluations are shown in Table 2. While there were no differences in total cholesterol and HDL cholesterol when olive oil periods were compared with MaxEpa periods, there was a significant decrease in triglycerides after 6 weeks of MaxEpa therapy.

Table 2 also displays the measurements of hemostat-

### Table 1 Baseline Characteristics of the Study Subjects

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age/Sex</th>
<th>Neurologic Deficit</th>
<th>C-T/Angiogram</th>
<th>Total Chol (mg%)</th>
<th>HDL Chol (mg%)</th>
<th>Triglycerides (mg%)</th>
<th>Bleeding Time (min)</th>
<th>Platelet Count* (per µl)</th>
<th>Factor VIII (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>71/M</td>
<td>Lt-sided weakness</td>
<td>Plaques — rt int carotid</td>
<td>189</td>
<td>48</td>
<td>82</td>
<td>5</td>
<td>437,000</td>
<td>208</td>
</tr>
<tr>
<td>2</td>
<td>73/F</td>
<td>Transient global amnesia</td>
<td>Normal</td>
<td>235</td>
<td>56</td>
<td>111</td>
<td>5½</td>
<td>423,000</td>
<td>140</td>
</tr>
<tr>
<td>3</td>
<td>67/M</td>
<td>Visual scotomata, Rt hand numbness (no history of migraine)</td>
<td>Normal</td>
<td>243</td>
<td>48</td>
<td>155</td>
<td>4½</td>
<td>410,000</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>72/F</td>
<td>Lt-sided weakness Vertigo</td>
<td>Rt basal ganglia infarct</td>
<td>348</td>
<td>24</td>
<td>419</td>
<td>8½†</td>
<td>363,000</td>
<td>92</td>
</tr>
<tr>
<td>5</td>
<td>69/M</td>
<td>Asymptomatic</td>
<td>Occluded rt carotid Stenotic lt carotid</td>
<td>212</td>
<td>41</td>
<td>103</td>
<td>4½</td>
<td>370,000</td>
<td>500</td>
</tr>
<tr>
<td>6</td>
<td>53/M</td>
<td>Rt arm weakness Visual blurring</td>
<td>Lt posterior cerebral infarct Lt occipital infarct</td>
<td>228</td>
<td>23</td>
<td>132</td>
<td>4½</td>
<td>454,000</td>
<td>92</td>
</tr>
<tr>
<td>7</td>
<td>59/M</td>
<td>Transient aphasia</td>
<td>Brain stem infarct</td>
<td>300</td>
<td>49</td>
<td>233</td>
<td>1½</td>
<td>575,000</td>
<td>156</td>
</tr>
<tr>
<td>8</td>
<td>62/M</td>
<td>Confusional episodes Lt-sided signs</td>
<td>Lt carotid plaques Rt basal ganglia infarct</td>
<td>177</td>
<td>40</td>
<td>65</td>
<td>3½</td>
<td>488,000</td>
<td>320</td>
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<tr>
<td>9</td>
<td>66/M</td>
<td>Rt-sided weakness Aphas</td>
<td>Lt int capsule infarct Plaque — Lt carotid bulb, occluded rt int carotid</td>
<td>245</td>
<td>56</td>
<td>263</td>
<td>4½</td>
<td>599,000</td>
<td>146</td>
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<tr>
<td>10</td>
<td>76/F</td>
<td>Lt-sided corticospinal signs</td>
<td>Rt cerebral infarct Rt carotid occlusion</td>
<td>254</td>
<td>37</td>
<td>125</td>
<td>6½</td>
<td>550,000</td>
<td>212</td>
</tr>
<tr>
<td>11</td>
<td>73/F</td>
<td>Bilateral Babinski signs</td>
<td>Cerebellar infarct</td>
<td>287</td>
<td>22</td>
<td>357</td>
<td>4</td>
<td>327,000</td>
<td>320</td>
</tr>
</tbody>
</table>

*In platelet-rich plasma.
†Recent aspirin ingestion.
TABLE 2 Cholesterol, Triglycerides, and Hemostatic Values in 11 Patients with Cerebrovascular Disease Receiving Olive Oil (O) or MaxEpa (M)

<table>
<thead>
<tr>
<th></th>
<th>Total Cholesterol (mg%)</th>
<th>Platelet Aggregation (ΔLT)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>O</td>
<td>M</td>
</tr>
<tr>
<td>Three weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>255 ± 49</td>
<td>264 ± 53</td>
</tr>
<tr>
<td>Six weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>244 ± 51</td>
<td>252 ± 51</td>
</tr>
</tbody>
</table>

Bleeding Time (min)                           | Collagen | ADP  | Arachidonate |
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>4 ± 1</td>
<td>26 ± 10</td>
<td>30 ± 12</td>
</tr>
<tr>
<td>M</td>
<td>4½ ± 1</td>
<td>28 ± 9</td>
<td>28 ± 8</td>
</tr>
<tr>
<td>p</td>
<td>0.023</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Six weeks                           | Collagen | ADP  | Arachidonate |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>5 ± 1</td>
<td>24 ± 13</td>
<td>30 ± 15</td>
</tr>
<tr>
<td>M</td>
<td>5 ± 1</td>
<td>29 ± 13</td>
<td>30 ± 15</td>
</tr>
<tr>
<td>p</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are means ± standard deviation.

*HDL = High Density Lipoprotein.
†MDA = Malondialdehyde.
NS = Non-Significant.

ic factors. After 3 weeks of MaxEpa treatment, there was a slight but significant prolongation of the bleeding time; however, at 6 weeks this difference between olive oil and MaxEpa treatment was no longer statistically significant. Platelet count and platelet aggregation to threshold concentrations of agonists were reduced during the period of MaxEpa administration, but not to a significant degree; the plasma concentrations of factor VIII-related antigen were unaffected. Only collagen-stimulated platelet malondialdehyde (MDA) production showed a significant change during MaxEpa therapy, and this was an increase over the values observed during the olive oil period.

Discussion

This study was performed because of reports that fish oil concentrates reduced serum cholesterol and inhibited platelet function. It was thought that these changes would be beneficial in patients with established atherothrombotic disease. However, it was found that the concentrate used in this study, MaxEpa, in a dose of 10 ml daily (1.8 G EPA), had only minimal, unsustained effects in the patients examined. Several possible reasons for this lack of efficacy may be enumerated.

Most important, the dose of MaxEpa may have been inadequate to effect cholesterol concentrations or platelet function. In one study, a reduction in serum cholesterol occurred with the equivalent of 10 G EPA ingested daily for 4 weeks. The inhibition of platelet activity observed by Dyerberg and Bang was observed with diets containing 5.8 G EPA. Similarly, the mackerel diets which significantly impaired platelet function and reduced platelet thromboxane production consisted of either 2–3 G EPA daily for 11 weeks or 7–11 G daily for 1 week. In the two trials using MaxEpa in the same dose (10 ml daily) as employed in this study, the bleeding time was not affected in one and only modestly prolonged in the other (5.1 to 5.7 min). Therefore, it may now be concluded that the dose of MaxEpa which will be required to consistently and significantly affect platelet function will be in excess of 1.8 G EPA. Such a dose will necessitate the ingestion of more than 10 capsules daily, which will probably prove to be impractical in most stroke patients. In our small study, 4 of the 18 patients initially enrolled in the trial had to drop out because they were unable to swallow even 10 capsules daily. An alternative would be the administration of the liquid oil. This poses a risk of aspiration and lipoid pneumonia in elderly, neurologically-impaired subjects, and was not used by us in this trial because of the difficulty of conducting a blinded study with a material which has such a pungent odor and distinctive flavor.

Secondly, the duration of MaxEpa therapy may have been inadequate. Saynor et al demonstrated a reduction in total cholesterol and an increase in HDL-cholesterol in patients taking MaxEpa for 2 years. While we considered prolonging the trial, the requirement for the daily ingestion of 10 capsules, the persistence of symptoms in two patients, the need to interdict the use of aspirin as a potentially effective agent in some patients with cerebral ischemic disease, and the demonstrated lack of effect on target laboratory parameters, all mandated a relatively short trial with a limited number of subjects.

There are a number of other factors which may account for the lack of observable changes in the parameters under study. Most previous trials were in healthy young volunteers; elderly patients with extensive atherothrombotic disease and abnormal platelet and lipid metabolism may be more resistant to dietary modifications. The very impressive changes in cholesterol and triglycerides summarized by Goodnight et al occurred with the feeding of unprocessed marine oils; MaxEpa is a commercially-prepared fish lipid concentrate and
therefore may be less potent than naturally-occurring products. Finally, our trial had a rigorous experimental design, a feature lacking in many of the earlier, unblinded studies. This design tended to ensure that other factors affecting platelet and lipid metabolism, such as diet and medications, would have little impact on the ultimate outcome of the investigation. We conclude that the daily ingestion of 10 MaxEpa capsules has little influence on such major risk factors as cholesterol concentration and platelet function in patients with atherothrombotic cerebrovascular disease.

Acknowledgment
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