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COMMUNICATION

A Preliminary Study on Intravenous Infusion of Sodium Eicosapentaenoate

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ABSTRACT

Eicosapentaenoic acid (EPA) and arachidonic acid (AA), made into sodium salt solution (50 μg/ml), were used for intravenous infusion. In a preclinical study in dogs, Na-EPA lowered the activity of transminases (glutamic pyruvic transaminase [GPT], glytamic oxaloacetic transaminase [GOT]); however, Na-AA increased the activity of GPT and GOT. In the clinical study, the numbers of leukocytes and lymphocytes of volunteers increased and remained at that level for 3 to 5 days after intravenous infusion. The study indicated that an intravenous infusion of Na-EPA may have anti-inflammatory and immunomodulatory effects.
Key Words: *AA; EPA; Fish oil; Intravenous infusion.*

INTRODUCTION

Fish oil is rich in *n*-3 polyunsaturated fatty acids of carbon-20 and carbon-22, especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The functions of metabolism and physiology of *n*-3 polyunsaturated fatty acids from fish oil are much different from those of *n*-6 fatty acids from plants and any other animals. In recent research on prostaglandin and bishomo-γ-linoletriene, the relationship between the metabolism of *n*-3 polyunsaturated fatty acids and life science has been indicated, which has also been used for research on its relation to decreased blood lipids (1), anti-inflammation, and antithrombus (2). In particular, as a presubstance of 3-prostaglandin and 5-bishomo-γ-linoletriene, EPA has received increased attention by medical researchers.

Since sodium fish liver oil, a clinical reagent that is rich in EPA and DHA, has been used as an injection in the esophagus vein to control and treat portal hypertension complicated by variceal hemorrhage (3), it is possi-

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ble to adjust eicosanoid in the body through intravenous infusion of Na-EPA. This research paper reports the results of intravenous infusion of Na-EPA in dogs and humans.

MATERIALS AND METHODS

The EPA (>99%) was made by the Research Center of Fishery Corporation (Japan). Arachidonic acid (AA; gas chromatography standard) was made by Fluka AG (Buchs, Switzerland).

For the preparation of Na-EPA and Na-AA, fatty acids were dissolved in 5 volumes of ethanol. Then, 1 N NaOH-ethanol was added precisely according to acid number. Nitrogen vapor was applied to the ethanol at 40°C. To make sodium fatty acid solution (25 mg/ml fatty acid), 0.9% NaCL was added. The final injection concentration will be 50 μg/ml of fatty acid in 0.9% NaCL.

For the intravenous infusion in the dog (8.10 kg weight), anesthesia was administered by injecting thiopentalum natricum, and a 500-ml (3 ml/min) intravenous infusion of Na-EPA and Na-AA was given through a forelimb. Blood was collected before and after infusion and was assayed according to blood chemical quota of humans. In humans, volunteers with low leukocyte counts (~4000/mm^3) were given a 500-ml (3 ml/min) intravenous infusion of Na-EPA and Na-AA through the forearm, and blood was collected and assayed.

RESULTS

Before and after intravenous infusion of Na-EPA and Na-AA in dogs, there was no change in the ratio of total protein, albumin, and globulin in blood and in the concentration of bilirubin and alkaline phosphatase, which indicated that intravenous infusion of Na-EPA and Na-AA did not result in hemolysis. A functional change of kidney and gall bladder was not found. However, the activities of glutamic pyruvic transaminase (GPT) and glytamic oxaloacetic transaminase (GOT) were affected. Na-EPA decreased the activity of transaminases, while Na-AA increased the activity of transaminases (see Table 1).

Before and after intravenous infusion of Na-EPA in humans, changes in the ratio of total protein, albumin, and globulin in blood and in the concentration of bilirubin, alkaline phosphatase, and calcium of blood cholesterol, fibrinogen, hemoglobin, and erythrocytes were not found. There was no change in the time of bleeding and plasma thromboplastin. The activity of transaminases did not show any change in volunteers. The only change found in humans was that lymphocytes increased significantly, which was accomplished by increase of leukocyte. The clinic data shows that, after intravenous infusion of Na-EPA, total leukocytes increased ($P < .05$), the numbers and percentage of lymphocytes increased ($P < 0.05$); the number of neutrophils remained unchanged, but the percentage decreased significantly ($P < .05$). After intravenous infusion of Na-EPA, the number and classification of leukocytes changed and remained for at that level for 3 to 5 days (see Table 2).

DISCUSSION

EPA and AA, as the components of membrane phospholipids of an organism, become free fatty acids by the reaction of phospholipidase A_2. Free fatty acids are metabolized to prostaglandin by cyclo-oxygenase and to bishomo-γ-linoletriene by lipid oxygenase. The anti-inflammation and antithrombus mechanisms of EPA and DHA are derived through the adjustment of the products of prostaglandin and bishomo-γ-linoletriene on platelets, vessel walls, and leukocytes (2).

The purpose of this experiment was to show that EPA was digested to 3-prostaglandin or 5-bishomo-γ-linole-

Table 1

Activity Change of Transaminases Before and After Intravenous Infusion of Na-EPA and Na-AA in Dogs (Mean ± SE)[a]

Enzyme	No. of Dogs	Na-AA		Na-EPA	
		Before	After	Before	After
GPT	6	Normal	98.2 ± 23.3[b]	Normal	Normal
GOT	6	56.6 ± 8.0	80.7 ± 5.6[b]	79.0 ± 10.9	44.9 ± 6.7[b]

[a] GPT, GOT assay according to clinic determination, with GPT below 40 as normal.
[b] $p < .05$.

Table 2

Before and After Human Intravenous Infusion of Na-EPA Changes of the Number and Classification of Leukocytes (Mean ± SE)

	Neutrophil		Lymphocyte		Total Numbers of Leukocytes
	Cells/mm^3	(%)	Cells/mm^3	(%)	
Before	2910.7 ± 260.0	69 ± 1.5	1230.7 ± 417.5	29.7 ± 2.1	4200 ± 318.3
After	3191 ± 54.2	55.7 ± 0.7[a]	2474.7 ± 37.9[a]	44.0 ± 2.7[a]	5716 ± 245.1[a]

[a] $P < .05$.

triene by enzymes through intravenous infusion of Na-EPA (free EPA: *R*-COO^-) to inhibit the metabolism of AA. Research has pointed out that, when sodium fish liver oil is injected into circulatory blood, free fatty acids will combine with albumin in blood immediately; no damage to the organs has been found. In recent years, Croset and Iagarde have studied the effect on the function of platelets in vitro through linkage of EPA (DHA)–albumin (4).

Intravenous infusion of fish oil emulsion has been studied (5), but it has been ignored that both plant oils and fish oils contain oleic acid (C18:1, *n*-9) and linolenic acid (C18:2, *n*-6), which result in lung damage, affect the blood kinetics of lung, and promote dyspnea during intravenous infusion (6–8).

In this research, AA increased the activity of GPT and GOP of dogs and EPA decreased the activity, which indicated that *n*-3 and *n*-6 fatty acid have a reverse effect compared to the activity of transaminases. It is possibly related to the osmosis of the membrane. LTC_4 and LTD_4, the products of bishomo-γ-linoletriene metabolism from AA, have 1000 times the osmosis of histamine. EPA inhibits the metabolism of AA, produces low activation of LTC_5 (leukotriene C_5) and LTD_5 (leukotriene D_5), and decreases the osmosis of the membrane. This is one of the anti-inflammatory mechanisms (3).

In human volunteers, an intravenous infusion of Na-EPA resulted in an increased number of leukocytes in the peripheral circulation. The reason is that the lymphocytes increased dramatically. The major function of lymphocyte is immunity. The research of Bjerve et al. indicated that patients who had a shortage of *n*-3 fatty acids had it made up by α-linolenic acid (C18:3, *n*-3) in 4 weeks, and the T lymphocytes doubled. If EPA was used, the T lymphocytes increased much more; however, the B lymphocytes were unchanged (9).

Further research expects to demonstrate that intravenous infusion of Na-EPA will be a new therapy for thrombosis, diabetes, cancer, and autoimmune system diseases (10).

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