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Case Report

Potential Effects of Eicosapentaenoic Acid Health Supplement Raffinee-Epagold® on Coronary Spastic Angina

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Received: February 11, 2018; **Published**: April 12, 2018

Abstract

Patients with coronary spastic angina (CSA) are sometimes refractory to adequate medical treatments or cannot tolerate such drugs due to their side effects. Herein, we report a patient with CSA who revealed the potential effects of eicosapentaenoic acid (EPA), an omega-3 polyunsaturated fatty acid, health supplement raffinee-epagold® (Orientalbio Co., Ltd., Tokyo, Japan) in reducing spasms.

Raffinee-epagold® was developed in a method that enabled extraction and purification of cis body EPA maintaining the three-dimensional structure and effective intestinal absorption. A 52-year-old man with a 6-year treatment history for CSA visited our office complaining of worsening chest oppression at rest in the early morning and at work as a public officer. He managed to tolerate only 200 mg of diltiazem hydrochloride R per day. Concomitant use of other medications was not feasible due to severe headaches. We showed the potential add-on effect of raffinee-epagold® (3 tabs per day which contains EPA: 302 mg, docosahexaenoic acid (DHA): 84.0 mg, vitamin E: 14.1 mg, vitamin C: 14.4 mg, vitamin B12: 1.2 μg) on this patient by the reduction of frequency in angina attacks and use of nitroglycerin.

Keywords: *Vasospastic Angina Pectoris; Eicosapentaenoic Acid (EPA); Side Effects; Headache; Supplement; Angina Pectoris*

Introduction

Coronary spastic angina (CSA) indicates a form of angina caused by coronary artery spasms defined as a condition, which are relatively large coronary artery running on the surface of the heart transiently exhibits an abnormal contraction, resulting in a dramatic reduction of coronary blood flow [1,2]. The prevalence of coronary spasms is higher in Japan and Korea than in Western countries, and Yasue., *et al*. reported that coronary spasms were documented in 40% of patients with angina pectoris who underwent coronary angiography in Japan [3]. Thus, effective treatments for CSA are mandatory. After definitively confirming the presence of positive coronary spasms, vasoactive drugs, such as long-acting calcium-channel antagonists, nitrates, and nicorandil, which are included as class I or IIa recommendations in the Japanese Circulation Society (JCS) guideline [1], are usually administrated. However, we encounter some CSA patients who are refractory to medical treatments or cannot tolerate such drugs due to their side effects. Herein, we report a case that revealed the potential efficacy of health supplement raffinee-epagold® (Orientalbio Co., Ltd., Tokyo, Japan) containing eicosapentaenoic acid (EPA), an omega-3 polyunsaturated fatty acid, in a patient with CSA.

Case Report

A 52-year-old man visited our office complaining of worsening chest oppression at rest in the early morning and at work as a public officer in January of 2017. His coronary risk factors included hyperlipidemia, former smoker, dyslipidemia, and type D personality. He had a 6-year history of medication for CSA ahead of this presentation. Diagnosis was only symptom-based and coronary organic stenosis was

denied by CT coronary angiography in 2011 and 2016 at another hospital. Because negative predictive value of CT coronary angiography for organic stenosis is high, we did not add invasive coronary angiography at the first presentation. He began exercising at a medical fitness club that is affiliated to our hospital to treat life-style-related diseases in September of 2016. He also attended nutrition education class in December of 2016. He had several problems which made his disease treatment refractory; severe headaches by vessel dilating drugs, mental stress, and drug allergies. His clinical course since attending our hospital is shown in Table 1. Doses of calcium channel blocker (Class I) and nicorandil (Class IIa) were initially increased according to the guideline of the JCS [1]. However, he could not tolerate the combination due to severe headaches. Sublingual nitroglycerin exaggerated the headaches. Angina attacks and headaches made him take a two-week break from work twice during the follow-up. He underwent invasive acetylcholine provocation test to confirm CSA after the first break from work. Prescription history is shown in Table 2. He could only continue taking long-acting diltiazem hydrochloride 200mg per day, although the headaches continued. Nicorandil and long-acting nitrate caused intolerable headaches. Benidipine hydrochloride previously caused a hepatic injury, thus, few drugs were tolerable for him. The frequency of the chest pain attacks and use of sublingual nitroglycerin decreased 21 days after starting raffinee-epagold®. The number of angina attacks improved from several attacks a month (1/16-2017-9/2/2017) to 0-1 a month (9/3/2017-1/12/2018) with add-on use of raffinee-epagold®. He now works in a good condition without taking a break.

Treatment period (days)	Frequency of angina attacks	Frequency of sublingual nitroglycerine	Medication dose (per day)	Clinical events
2017				
1/16-1/20 (5)	3	3	Diltiazem hydrochloride R 100 mg Nicolandil 10 mg	
1/21-2/3 (15)	2	2	Diltiazem hydrochloride R 200 mg Nicolandil 15 mg	
2/4-2/19 (16)	3	3	Diltiazem hydrochloride R 200 mg Nicolandil 15 mg	2/15~2/29 break from a work
2/20-2/24 (5)	2	2	None	Severe headaches
3/10	0	0		Acetylcholine provocation test positive
2/25-3/24 (32)	4	4	Diltiazem hydrochloride R 200 mg	
3/25-4/22 (29)	4	3	Diltiazem hydrochloride R 200 mg	
4/23-5/10 (18)	2	2	Diltiazem hydrochloride R 200 mg	
5/10-5/24 (15)	1	1	Diltiazem hydrochloride R 200 mg Diazepam	
5/25-6/16 (23)	2	2	Diltiazem hydrochloride R 200 mg	
6/17-7/5 (19)	4	7	Diltiazem hydrochloride R 200 mg	7/3~ 7/17 break from a work
7/6-7/14 (9)	1	1	Diltiazem hydrochloride R 200 mg	
7/15-7/29 (15)	6	6	Diltiazem hydrochloride R 200 mg	
7/30-8/26 (28)	2	2	Diltiazem hydrochloride R 200 mg Nicolandil 15 mg	Emergency office visit (troponin I negative)
8/27-9/16 (21)	0	0	Diltiazem hydrochloride R 200 mg Raffinee-epagold® 3Tabs (9/3~)	
9/17-10/14 (28)	1	1	Diltiazem hydrochloride R 200 mg raffinee-epagold® 3Tabs	
10/15-11/11 (28)	1	1	Diltiazem hydrochloride R 200 mg raffinee-epagold® 3Tabs	
11/12-12/9 (28)	0	0	Diltiazem hydrochloride R 200 mg raffinee-epagold® 3Tabs	
12/10-1/12 (34)	1	1	Diltiazem hydrochloride R 200 mg raffinee-epagold® 3Tabs	

Table 1: *Clinical course since visit to our hospital.*

Prescribed drugs, frequency of angina attacks, and clinical events are shown. These were evaluated at every visit to clinic. He took a two-week break from work twice before raffinee-epagold®. Number of angina attacks decreased from several attacks a month (1/16-2017-9/2/2017) to 0-1 attack a month (9/3/2017-1/12/2018) with the use of raffinee-epagold®.

Allowed	Not allowed
Diltiazem hydrochloride (sustained-release tablet)	Benidipine hydrochloride
	Isosorbide dinitrate
	Nitroglycerin
	Nicorandil

Table 2: *Prescription History of Anti-anginal Drugs.*
Only sublingual tablet is tolerable always with headache medicine.

Discussion

We experienced a patient with CSA in whom raffinee-epagold® seemed to be effective as an add-on treatment for refractory CSA despite the use of a calcium channel blocker in reducing the frequency of angina attacks and use of nitroglycerin.

Three tabs of raffinee-epagold® 300 (daily standard dose: 1.65g) contains; calorie 10.56 kcal, protein 0.47g, lipid: 0.88g, carbohydrate: 1.65g, Na: 1.62 mg, EPA: 302 mg, docosahexaenoic acid (DHA): 84.0 mg, vitamin E: 14.1 mg, vitamin C: 14.4 mg, vitamin B12: 1.2 μg). EPA contained in raw fish has a high inhibiting ability for vascular spasm owing to its three-dimensional cis body structure. However, once it is heated, its structure would be broken and would have a decreased ability. Raffinee-epagold®, which is a nutrient function food, was developed in a method that enabled extraction and purification of cis body EPA maintaining the three-dimensional structure and effective intestinal absorption after oral administration by promoting bile excretion with several auxiliary components. Yamaguchi university (Professors Sei Kobayashi and Hiroko Kishi) obtained two patents for these inventions in Japan.

Rho-kinase is an important molecular switch that controls the contraction and relaxation of vascular smooth muscle independently of the intracellular Ca^{2+} concentration that maintains normal vessel contraction. Upon stimulation by a vasopressor substance, Rho, a low-molecular-weight G protein, is activated via the G protein-coupled receptor (GPCR), and Rho-kinase, one of its target proteins, is activated. The activated Rho-kinase phosphorylates the myosin-binding subunit (MBS) of myosin light chain phosphatase (MLCPh) to inhibit its activity. As a result, the balance between myosin light chain kinase (MLCK) and MLCPh activity is lost and MLCK becomes dominant, which promotes the phosphorylation of MLC and induces excessive contraction of vascular smooth muscle (Ca^{2+}-sensitization) [4,5].

Because there are many physiological stimuli as GPCR agonists in Ca^{2+}-sensitization of vascular smooth muscle cells, Shirano., et al. [6] suspected the existence of the non-Rho/GPCR related signaling molecule and identified sphingosylphosphorylcholine (SPC) as a new molecule causing Ca^{2+}-sensitization. SPC is generated by N-deacylation of sphingomyelin, one of the most abundant lipids in the cell membrane, and is a phospholipid mediator in blood plasma and has a physiopathological role in the regulation of the heart [7]. Shirano and Kobayashi., *et al*. previously reported that EPA inhibits SPC-induced Ca^{2+}-sensitization of vascular smooth muscle contraction by targeting Src family protein kinases, including Fyn, without any influence on intracellular Ca^{2+} concentration that normalize vascular contractions [6].

For patients whose control of coronary spasm with calcium channel blockers or nitrates is not possible due to the complex pathophysiology of coronary spasm or intolerable due to side effects, prophylactic medications with different actions are required.

Increased activity of Rho-kinase causes hypercontraction of vascular smooth muscle and has been implicated as playing a pathogenetic role in divergent cardiovascular diseases, such as coronary artery spasms.

Shimokawa., *et al.* [8] revealed that hydroxyfasudil-sensitive Rho-kinase-mediated pathways appear to mediate the enhanced MLC phosphorylations and play a central role in the pathogenesis of coronary artery spasm. Matsumoto., *et al*. [9] showed that fasudil, a selective Rho-kinase inhibitor (Y-27632), was effective in preventing acetylcholine-induced coronary artery spasm and resultant myocardial ischemia in patients with vasospastic angina. However, fasudil does not have adequate evidence and is not yet being utilized clinically for CSA in Japan. Raffinee-epagold® is expected to act as another inhibitor of the Rho-kinase pathway for patients with CSA.

Endothelial dysfunction is also related to the coronary vasospasm [3]. It has been reported that the small GTPase RhoA directly suppress nitric oxide (NO) production in the endothelium through reduction of both eNOS activity and gene expression [10]. Studies have also shown that inhibition of RhoA leads to the activation of the Akt and eNOS in endothelial cells [11]. In this regards, raffinee-epagold® might be advantageous to prevent coronary spasm by improving endothelial function.

Limitations

First, raffinee-epagold® also contains vitamins C and E (class IIb treatment in JCS guideline) that have evidence for CSA treatment [12-14]. Although the doses of vitamins C and E in raffinee-epagold® are appropriate for prevention of coronary vasospasm or not is unknown, we cannot completely exclude the possibility. Secondary, it is intrinsically difficult to reveal the effectiveness of drugs by only subjective symptom.

Conclusion

The potential add-on effect of raffinee-epagold® is shown on a patient by the reduction of frequency in angina attacks and use of nitroglycerin.

Conflict of Interest

I declare that there is no conflict of interest.

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Volume 5 Issue 5 May 2018