The effect of a newly developed ointment containing eicosapentaenoic acid and docosahexaenoic acid in the treatment of atopic dermatitis

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Abstract : While various therapeutic modalities have been tried for atopic dermatitis (AD), numerous obstinate cases exist in which sufficient effects cannot be obtained. Therefore, we developed and prepared an ointment containing docosahexaenoic acid and eicosapentaenoic acid as a topical therapeutics for AD. We applied this ointment to 64 patients with AD (aged between 2 months and 29 years) who showed poor responses to conventional therapies and obtained satisfactory results. This ointment is considered a new topical preparation for AD. J. Med. Invest. 46 : 173-177, 1999

Key words **:** *atopic dermatitis, docosahexaenoic acid, eicosapentaenoic acid*

INTRODUCTION

Various therapeutic approaches have been recently made for atopic dermatitis (AD) because of the marked increase in the number of patients with AD and the appearance of numerous severe cases. Nevertheless, there are many refractory cases in which sufficient effects have not been obtained.

We developed an ointment containing eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) as a topical preparation for AD (1). We applied this ointment to 64 patients with AD who did not show improvement of symptoms by conventional treatments and obtained satisfactory results.

SUBJECTS

The subjects were 64 patients with AD (infancy 28, early childhood 15, later childhood 10, adolescence 5 and adulthood 6) who were treated topically with our newly developed EPA/DHA-containing ointment. The diagnosis of AD was made according to the Japanese Dermatological Association Criteria (2). These patients previously showed poor responses to conventional treatments including dietetics, oral administration of anti-allergic agents and application of topical preparations such as topical steroids or topical non-steroidal antiinflammatory drugs. We provided sufficient information concerning the ointment to all patients and obtained their consent to participate in the study.

Received for publication January 19, 1999 ; accepted April 6, 1999.

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MATERIAL

EPA/DHA containing ointment : EPA and DHA were extracted and purified from fish oils as a powdered product (N-Neopowder DHA20, NOF Co., Ltd.). Although the powder itself was stable for 8 weeks at room temperature, the patients were requested to store the ointment at 4°C and to discard it 4 weeks after preparation because its stability had not been fully examined (the product showed discoloration after several months). This ointment was prepared so that it contained a hydrophilic ointment base, 1.2 % DHA and 0.6 % EPA.

METHOD

The patients were basically treated by the EPA/

DHA-containing ointment alone. Those who had been given dietetics or oral administration of anti-allergic agents in other hospitals continued to these treatments while the drugs for topical use were replaced by the EPA/DHA-containing ointment. The ointment was applied to the target lesion 2 or 3 times a day and the effects were evaluated after 4 weeks of treatment. A dermatologist assisted with the evaluation. Skin symptoms were categorized into erythema, papule, squama, itching, thickening, crust and erosion, and the severity of each symptom was scored as follows : 3 points represented a severe lesion, 2 points a moderate lesion, 1 point a mild lesion and 0 point indicated no symptom. Then, the efficacy was evaluated by an increase or decrease in the score before and after the treatment. If some skin symptoms appeared in several sites in the same patient, each lesion was evaluated separately. If a symptom was absent (0 score) before and after the treatment, that lesion was excluded from evaluation. WILCOXON 's one-sample test was employed for statistical analysis.

RESULTS

1) Comparative study between the EPA/DHA-containing ointment and the placebo (Table 1)

Table 1. Efficacy of EPA/DHA Ointment in Atopic Dermatitis Patients

Symptoms	No.of patients evaluated[a)]	Group	Treatment period	Symptom score				Improvement in the degree of skin symptoms after 4 weeks of treatment[b)]							Efficacy rate[c)]	Statistical analysis (Wilcoxon one-sample test)
				0	1	2	3	−3	−2	−1	0	1	2	3		
Erythema	11	EPA/DHA	Pretreatment	0	5	6	0	0	4	5	2	0	0	0	9/11 (81.8%)	**
			4 weeks	7	4	0	0									
		Control	Pretreatment	0	7	3	1	0	0	3	6	2	0	0	3/11 (27.3%)	NS
			4 weeks	3	2	5	1									
Papule	12	EPA/DHA	Pretreatment	0	5	7	0	0	4	6	2	0	0	0	10/12(83.3%)	**
			4 weeks	7	5	0	0									
		Control	Pretreatment	0	9	2	1	0	0	3	8	1	0	0	3/12 (25.0%)	NS
			4 weeks	2	6	4	0									
Squama	5	EPA/DHA	Pretreatment	0	4	1	0	0	1	4	0	0	0	0	5/5 (100.0%)	NS[d)]
			4 weeks	5	0	0	0									
		Control	Pretreatment	3	1	1	0	0	0	0	2	3	0	0	0/5 (0.0%)	NS
			4 weeks	0	4	1	0									
Itching	10	EPA/DHA	Pretreatment	0	7	2	1	0	2	7	1	0	0	0	9/10 (90.0%)	**
			4 weeks	7	3	0	0									
		Control	Pretreatment	1	7	1	1	0	0	4	3	3	0	0	4/10 (40.0%)	NS
			4 weeks	3	3	4	0									
Crust	1	EPA/DHA	Pretreatment	0	1	0	0	0	0	1	0	0	0	0	1/1 (100.0%)	NS[d)]
			4 weeks	1	0	0	0									
		Control	Pretreatment	0	1	0	0	0	0	0	1	0	0	0	0/1 (0.0%)	—
			4 weeks	0	1	0	0									

Each value indicates the number of patients. ** : p≦0.01, NS : p>0.05 NS = Not Significant

a) The patients with no abnormal skin symptoms pre-and post-treatment were not included.
b) Improvement in the degree of skin symptoms = (symptom score after 4 weeks of treatment)−(symptom score of pretreatment) [−] represents improvement, [0] represents no change, [+] represents progressive disease.
c) [Total No. of improved cases (score : −3〜−1)]/[No. of patients evaluated]. Numbers in parentheses indicate improvement rates (%) VS total No. of patients.
d) Due to the small number of patients treated.

Therapeutic effects of the test ointment and the placebo (a hydrophilic-ointment base) were compared in 12 patients with AD. The study was conducted in such a way that the test ointment and placebo were applied to lesions on the left and right arms or the left and right legs of 12 patients, for 2-7 weeks. The degrees of improvement of skin symptoms were compared before and after the treatment. Since 2 of the 7 categories of skin symptoms were not observed either before or after the treatment, 5 categories were compared. The test ointment showed more than 80% improvement in all 5 categories and the efficacies were significant by WILCOXON 's one-sample test. On the other hand, the placebo showed lower rates of improvement between 0 and 40 % and some of the lesions were aggravated. No significant difference was detected before and after the treatment in the placebo treated lesions.

2) Change in skin symptoms (Table 2)

Change in skin symptoms before and after the treatment was shown with scores (Mean±S.D.). Scores after 4 weeks of treatment decreased in all 7 categories compared to the starting time indicating improvement of skin symptoms. Erythema, papule, squama, itching and thickening were significantly decreased as shown by WILCOXON 's one-sample test. There was no significant difference in the degrees of improvement of crust and erosion, probably due to the small number of eligible subjects.

3) Degree of improvement of skin symptoms in patients with AD (Table 3)

Distribution of the number of lesions with respect to the severity of symptoms (0, 1, 2 and 3 points) showed distinct shifts to lower scores for all 7 categories 4 weeks after the start of treatment indicating improvement. When the degree of improvement of symptoms 4 weeks after the start of treatment was compared at each site, the highest improvement was shown in erosion followed by erythema, papule, thickening, squama, crust and itching. However, concerning erosion and crust, the numbers of sites were small and, therefore, no significant differences were detected by WILCOXON 's one-sample test.

DISCUSSION

Based on immunohistological study using a patch test with a mite antigen, Tanaka *et al*. reported (3) that histamine, platelet activating factor (PAF), eosinophilic chemotactic factor (ECF-A) and some arachidonic acid (AA) metabolites [leukotriene (LT) B_4, LTC_4] released from mast cells as well as eosinophils were involved in the onset of AD. Fogh *et al*. (4) revealed that the concentrations of prostaglandin E_2, LTB_4 and 12/15 monohydroxy acid, which are AA metabolites,were increased in AD lesions and in the skin close to the lesions compared to the healthy skin of patients with AD or the skin of healthy subjects. Ruzicka *et al*.(5) demonstrated using the suction blister method that the LTB_4 level in lesions of patients with AD was higher than that in the healthy skin of the same patients. Thus, AA metabolites in the skin were suspected to be involved in the mechanism of the onset of AD.

Table 2 : Improvement of Skin Symptoms by EPA/DHA Ointment

Symptoms	No.of target lesions	Symptom score (mean±SD)		Statistical analysis (Wilcoxon one-sample test)
		Pretreatment	After 4 weeks of treatment	
Erythema	78	1.63±0.65	0.62±0.76	**
Papule	71	1.69±0.58	0.77±0.72	**
Squama	30	1.60±0.77	0.77±0.73	**
Itching	65	1.88±0.67	1.17±0.84	**
Thickening	11	1.64±0.67	0.45±0.52	*
Crust	16	1.38±1.02	0.63±0.81	NS
Erosion	6	2.00±0.63	0.33±0.52	NS

** : p≦0.01, * : p≦0.05, NS : p>0.05

NS = Not Significant

[Score of skin symptoms : 3 =severe, 2 =moderate, 1 =mild, 0=normal]

Table 3 : Improvement of Skin Symptoms by EPA/DHA Ointment

Symptoms	No.of symptom lesions	Treatment period	Symptom score				Improvement in the degree of skin symptoms after 4 weeks of treatment[a]							Total No.of Improved lesions[b]	Statistical analysis (Wilcoxon one-sample test)
			0	1	2	3	−3	−2	−1	0	1	2	3		
Erythema	78	Pretreatment	0	36	35	7	2	19	40	12	5	0	0	61/78 (78.2%)	**
		4 weeks	42	25	10	1									
Papule	71	Pretreatment	0	26	41	4	2	9	43	15	2	0	0	54/71 (76.1%)	**
		4 weeks	28	31	12	0									
Squama	30	Pretreatment	1	14	11	4	1	5	13	10	1	0	0	19/30 (63.3%)	**
		4 weeks	12	13	5	0									
Itching	65	Pretreatment	2	13	41	9	1	5	30	24	3	2	0	36/65 (55.4%)	**
		4 weeks	16	24	23	2									
Thickening	11	Pretreatment	0	5	5	1	0	6	1	4	0	0	0	7/11 (63.6%)	*
		4 weeks	6	5	0	0									
Crust	16	Pretreatment	3	7	3	3	2	4	3	4	2	0	1	9/16 (56.3%)	NS
		4 weeks	8	7	0	1									
Erosion	6	Pretreatment	0	1	4	1	1	3	1	1	0	0	0	5/6 (83.3%)	NS
		4 weeks	4	2	0	0									

** : $p \leqq 0.01$, * : $p \leqq 0.05$, NS : $p > 0.05$
NS = Not Significant

Figures in each column indicate the number of target lesions.
a) Improvement in the degree of skin symptoms = (symptom score after 4 weeks of treatment)−(symptom score of pretreatment)
[−] represents improvement, [0] represents no change, [+] represents progressive disease.
b) [Total No. of improved lesions (score : −3〜−1)]/[No. of symptom lesions]
Numbers in parentheses indicate improvement rates (%) VS total No. of lesions.

It has been reported that metabolic enzymes such as lipoxygenase and cyclooxygenase are common to the AA cascade and EPA cascade and, moreover, EPA is superior to AA as a substrate for these common enzymes (6). Therefore, administration of EPA may competitively inhibit the progress of the AA cascade through common enzymes. It has been revealed that in the EPA cascade, the majority advances to the LTB_5 course and rarely to the LTC_5 course (7) and biological activity of LTB_5 is extremely weak compared to AA-derived LTB_4 (8). Furthermore, EPA metabolites may inhibit the activity of AA metabolites competitively through target cell receptors. Therefore, EPA administration was considered to inhibit the production of AA metabolites as well as the appearance of their effects. In addition DHA, which is an ω-3 unsaturated fatty acid similar to EPA, was reported to inhibit chemical mediators such as LT and PAF (9).

Thus, we prepared an EPA and DHA containing ointment and applied it to patients with refractory AD. However, two major questions arose concerning the topical use of EPA and DHA. 1) Are EPA and DHA absorbed percutaneously ? and 2) If EPA or DHA is absorbed percutaneously, are these compounds absorbed by target cells ?. Regarding the first question, the skin of a patient with AD seems to readily absorb EPA and DHA in the ointment since it has been reported that unlike healthy skin, numerous minute apertures and grooves as well as cellular gaps exist in the skin of patients with AD due to damage to the skin-barrier system (10). Concerning the second question, it has been reported that oral administrations of EPA and DHA in humans resulted in an increase in the EPA level and a marked decrease in the AA content in leukocytes (11), or in an increase in the EPA content and inhibition of production and release of AA metabolites including LTB_4 (12). Based on these results, we proposed that an EPA and DHA-containing ointment would be effective for patients with AD.

A total of 125 patients with AD visited our department for treatment with the EPA/DHA-containing ointment because of poor responses to

conventional treatments. Of these, 64 patients who were treated with the ointment for more than 4 weeks, were employed to assess the effect of the ointment. The other 61 patients were excluded because of exacerbation of AD after cessation of steroid therapy. The therapeutic effects were evaluated 4 weeks after the start of treatment and significant improvement was observed for all skin symptoms including erythema, papule, squama, itching, thickening, crust and erosion. The results of comparative examination between the EPA/DHA-containing ointment and the ointment base (Table1) indicated that improvement of symptoms by the EPA/DHA-containing ointment was not due to the ointment base but attributable to EPA and DHA. Although some cases showed aggravation of symptoms excluding thickening and erosion, this phenomenon seemed to be derived from violent scratching. No other adverse reaction was observed. In this study, only 64 subjects were examined and the observation period was short (4 weeks). Therefore, further examination is needed to confirm the efficacy, adverse reactions and the time of discontinuation of treatment. However, our findings suggest that the EPA/DHA-containing ointment for topical use is a promising, novel therapeutics for AD.

ACKNOWLEDGEMENTS

We express our deep gratitude to Dr. Kozo Yoshihara and the staff of the Pharmaceutical Section of Kagawa Prefectural Tsuda Hospital for their cooperation in preparing the ointment and to Dr. Naoyuki Uchida of the Department of Dermatology, The University of Tokushima School of Medicine, for helping us to examine the course of treatment.

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