Influence of Gamma linoleic acid (Epogam) on the Skin Surface Conditions of Atopic Dermatitis

Hyoun Seung Lee, M.D., Kyoung Chan Park, M.D., Kyu Han Kim, M.D.

Department of Dermatology, Seoul National University College of Medicine, Seoul, Korea

Background **: Gamma linoleic acid (GLA, Epogam) is considered a safe and effective modality in the treatment of atopic dermatitis (AD) in which impaired function of the enzyme, delta-6-desaturase, has been reported to result in reduced levels of GLA, desaturated fatty acids.**

Objective **: We performed this study to observe the changes of skin surface conditions measured objectively by bioengineering methods in relation to clinical improvement after treatment with GLA (Epogam®) in children with AD.**

Methods **: Thirty-four children with AD were treated with GLA (Epogam®) and evaluated with clinical parameters. The changes of skin surface conditions were monitored by non-invasive experimental instruments.**

Results **: There was a significant decrease of transepidermal water loss (TEWL) and gradual improvements in clinical severity after 12 weeks of GLA (Epogam®) treatment. The change of skin surface pH was statistically significant on the antecubital fossa and abdomen except the popliteal fossa. The other parameters including skin surface hydration and skin surface lipid did not show consistent changes.**

Conclusion **: Clinical improvement of AD with GLA (Epogam®) seemed to be achieved by the reduction of TEWL. (Ann Dermatol 12(4) 238~242, 2000).**

Key Words : Atopic dermatitis, GLA (Epogam®), Transepidermal water loss

Atopic dermatitis (AD) is characterized by hypersensitivity reaction with increased IgE production, higher susceptibility to skin infection with depressed cell-mediated immunity[1,2]. However, the most prominent finding of AD is pruritic sensation and this is frequently accompanied by a dry skin with increased transepidermal water loss (TEWL). Recently, altered fat metabolism has been reported, as linoleic acid tends to be increased whereas the unsaturated fatty acids, such as gamma-linolenic acid (GLA) and arachidonic acid show decreased amounts in the plasma[3], monocytes[4], red blood cells4 and epidermis[5] of patients with AD.

GLA has been focused as a new therapeutic approach of AD. The major component of Epogam® is GLA (C18: 3n-6) extracted from the selected strains of evening primrose *(Oenothera spp.)*, which may increase GLA and its metabolites in atopic patients.

This study was designed to observe the changes of various skin surface conditions, which could be assessed by using non-invasive experimental instruments, as well as the clinical effects after oral supplement of GLA (Epogam®) in the treatment of AD.

MATERIALS AND METHODS

Thirty-four children (equal numbers of each sex,

Received November 10, 1999.
Accepted for publication Apeil 7, 2000.
Reprint request to :Kyu Han Kim, M.D., Department of dermatology, Seoul National University College of Medicine, 28 Yongon-dong, Chongno-gu, Seoul 110-744, Korea
e-mail: kyuhkim@snu.ac.kr.
Tel) (02) 760-2418/ Fax) (02) 742-7344
*This work has been supported by grants from the Handok pharmaceuticals Co., LTD in Korea(1998).

mean age 6.4 years) were treated with Epogam® containing GLA at a dosage of 160mg twice a day. All patients were diagnosed as AD based on the criteria of Hanifin and Rajka[6]. The patients were treated with GLA (Epogam®) for 12 weeks and were assessed by the same dermatologist before treatment, 4 weeks and 12 weeks after treatment. They were otherwise healthy without any significant medical history and written consent was obtained in each case. This study was approved by the Institutional Review Board of our hospital. All patients were treated exclusively with GLA (Epogam®) and were strictly forbidden to use any other medication or preparation including topical emollients.

The clinical evaluation parameters were categorized into severity criteria and topography item. The severity criteria included erythema, induration/papulation, pruritus/excoriation, lichenification, scale/dryness, and erosion/oozing/weeping and the patients were scored as 0 (none), 1 (mild), 2 (moderate), and 3 (severe) based on their severity. The extent of AD, topographic item, was evaluated by the percentage of the involved portion in 10-body areas respectively; scalp, face, anterior trunk, posterior trunk, arms, hands, buttocks, legs, knees, and feet. The scoring system for extent on each site was 0 (none), 1 (<10%), 2 (10-30%), and 3 (>31%). The total severity score was defined as the sum of clinical severity scores and topographic item. All subjects were considered to have a mild to moderate degree of AD based on these evaluation criteria.

The changes of skin surface conditions were also monitored before treatment, 4 weeks and 12 weeks after treatment by noninvasive experimental instruments. We used two apparatus to evaluate epidermal hydration; Skincon-200® (I.B.S. Co. Ltd., Shizuokaken, Japan) by measuring the conductance of the skin and Corneometer CM 820® (Courage Khazaka GmbH, Cologne, Germany) by measuring the electrical capacitance of the skin. To measure TEWL and the skin surface pH, we used the Tewameter TM 210® (Courage Khazaka GmbH) and the Skin-pH-METER PH 900 (Courage Khazaka GmbH), respectively. Sebumeter SM 810® (Courage Khazaka GmbH) was used to measure the content of skin surface lipid. Procedures were performed as described previously[7-10]. Three predilection sites of AD were selected for measurements; antecubital fossa, abdomen, and popliteal fossa. All parameters were measured at the same sites each time under constant environmental circumstances (room temperature 20-22℃ and relative humidity 40-50 %). The patients were not allowed to take a shower on testing days and took rest for a minimum of 30 minutes in the room prior to measuring procedures. The difference between baseline and 12 weeks of GLA (Epogam®) treatment was analyzed by the paired t-test and $p< 0.05$ was considered significant.

RESULTS

Thirty children completed this trial and were evaluated. The results are summarized in Tables 1 and 2. The patients showed gradual improvements in clinical severity based on the assessment of severity criteria, topographic items and their sum, total severity score. The reduction in these three parameters at 12 weeks was statistically significant compared with the baseline ($p<0.0001$). Among the noninvasive methods used, only the values of Tewameter (TEWL) revealed significant reduction on all tested sites (antecubital fossa, abdomen, and popliteal fossa; p=0.002, 0.0005, 0.0486, respectively). The hydration values of the skin surface measured by both Corneometer and Skincon-200® were not significantly increased. However, the values of hygrometer on the popliteal

Table 1. Summary of the changes in clinical severity scores from baseline to 12 weeks in response to GLA(Epogam®)

Assessment	baseline	4 weeks	12 weeks	P-value*
Severity criteria	6.7±2.9	5.8±3.4	3.5±3.3	$p<0.0001$
Topographic item	8.1±5.2	6.4±4.6	4.1±4.7	$p<0.0001$
Total severity score	14.9±7.7	12.2±7.7	7.6±7.8	$p<0.0001$

* Significance between baseline and 12 weeks of GLA(Epogam®) treatment
Each value represents mean±S.D

Annals of Dermatology
Vol. 12, No. 4, October 2000

Table 2. Summary of the changes in skin surface characteristics from baseline to 12 weeks in response to GLA (Epogam®)

	Corneometer (a.u)	pH-meter	TEWL (g/hm2)	Hygrometer ($\mu\sigma$)
antecubital fossa				
baseline	83.1±16.7	5.0±0.6	20.5±13.7	88.1±63.4
4 weeks	93.2±19.3	5.1±0.6	14.6±5.0	116.6±97.5
12 weeks	80.5±10.3	5.3±0.4	12.2±4.4	79.8±56.5
P-value*	p=0.4048	p=0.0003	p=0.002	p=0.596
abdomen				
baseline	70.1±15.4	5.0±0.7	9.8±5.0	38.2±30.3
4 weeks	80.1±20.1	5.1±0.7	7.0±2.2	55.2±50.7
12 weeks	68.4±10.7	5.4±0.5	6.2±2.7	37.2±35.6
P-value*	p=0.53	p=0.0118	p=0.0005	p=0.9107
Popliteal fossa				
baseline	79.7±22.3	5.1±0.8	20.8±23.1	75.5±62.5
4 weeks	89.5±18.5	5.1±0.6	14.2±5.4	83.8±76.1
12 weeks	77.1±11.1	5.3±0.4	12.3±7.9	48.8±40.3
P-value*	p=0.4749	p=0.2252	p=0.0486	p=0.0305

*; Significance between baseline and 12 weeks of GLA(Epogam) treatment
Each value represents mean±S.D

area showed significant increase. The skin surface pH became higher within acidic range on all three evaluated sites and its change was statistically significant on the antecubital fossa and abdomen (p=0.0003, p=0.0118, respectively). The level of skin surface lipid measured by Sebumeter was significantly low, but concerning the fact that there were obvious inter-measurement differences, the data was considered to be unreliable (data not shown). A few patients complained of the unpleasant tastes from oily constituents of GLA (Epogam®), but there were no side effects resulting in the withdrawal of medication.

DISCUSSION

The abnormal lipid and fatty acid patterns in the blood and epidermis of atopic patients may play a role in the pathogenesis of the disease. Increased levels of linoleic acid and deficiencies of 6-desaturated ω-6-fatty acids (GLA, dihomo-GLA, and arachidonic acid) have been observed in variable specimens from patients with AD[3-5,11]. These alterations may have attributed to the defective function of the enzyme, delta-6-desaturase, which is responsible for the conversion of linoleic acid to GLA[3] and this may be related to the immunological alterations in AD through the deficient conversion of n-6 fatty acids to prostaglandin E1 (PGE1) in mononuclear cells of AD patients[4,12]. Melnik et al.[13] demonstrated that PGE1 and PGE2 had a suppressive effect on *in vitro* IgE synthesis of mononuclear cells in patients with AD. This abnormal lipid and fatty acid pattern of AD is the target of therapeutic approach with oral supplement of fatty acid, GLA (Epogam®). Supplementation of evening primrose oil rich with n-6 fatty acids including GLA resulted in a rise in the ratio of n-6 to monounsaturated fatty acids in both lesional and lesion-free epidermis[14]. Some authors have reported that there was a positive correlation between improvements in clinical score and a rise in the fatty acid (dihomo-GLA and arachidonic acids) levels after treatment with GLA (Epogam ®)[15]. Numerous papers stating excellent outcomes have been reported on the use of GLA (Epogam) in adults, while the studies about therapeutic effects on children with AD have been quite limited[16,17]. We tried to correlate the beneficial effect of GLA (Epogam®) on AD children with the changes of skin surface characteristics monitored objectively by bioengineering methods.

Generally the barrier function of atopic epidermis is disturbed in contrast to a soft, smooth, well-

moisturized normal skin. TEWL was found to be increased in eczematous skin and in clinically normal skin of atopics on predilection areas[18]. The water content of the horny layer measured with the Corneometer was decreased in dry atopic skin[19]. The level of ceramides, major components of epidermal lipids, was reported to be significantly lower in atopic epidermis compared with that of the normal skin and the level of a certain ceramide (ceramide 3) was significantly correlated with the TEWL impairment[20]. Therefore it is suggested that a decrease in ceramides in the strautm corneum may be involved in epidermal barrier function impairment in AD.

In our study, the level of TEWL was significantly reduced after 12 weeks of treatment with GLA (Epogam®). Clinical severity score and the level of TEWL showed a similar pattern of reduction. Although this was not a study of double-blind, placebo-controlled design, we could minimize seasonal variability through measuring under constant ambient circumstances. The study was performed within a relatively short period of time from the end of spring to autumn and we do not think that reduced TEWL after GLA (Epogam®) treatment was the result of either a seasonal effect or spontaneous regression of the disease. Although skin pH was slightly raised on antecubital fossa and abdomen after GLA (Epogam®) treatment, we did not think this change of pH could contribute to the clinical improvement. However, the measurements of both Skincon-200® and Corneometer representing epidermal hydration status were not significantly changed. Contrary to our expectation, the level of skin surface lipid measured by Sebumeter did not show any consistent results.

This study provides the evidence that GLA (Epogam®) produces a favorable response partly through reducing TEWL. Based on the reports of positive correlation between higher fatty acid level in plasma, epidermal phospholipids and improved clinical finding[15], we suggest that clinical improvement and reduced TEWL may be associated with the increased level of fatty acids in the epidermis of AD after oral supplementation with evening primrose oil. The exact mechanism how fatty acid change in epidermal phospholipids affects TEWL should be further evaluated.

REFERENCES

1. Cooper KD: Atopic dermatitis: recent trends in pathogenesis and therapy. J Invest Dermatol 102:128-137, 1994.
2. Hanifin JM: Immunologic aspects of atopic dermatitis. Dermatol Clin 8:47-50, 1990.
3. Manku MS, Horrobin DF, Morse NL et al.: Essential fatty acids in the plasma phospholipids of patients with atopic eczema. Br J Dermatol 110:643-648, 1984.
4. Lindskov R, Holmer G: Polyunsaturated fatty acids in plasma, red blood cells and mononuclear cell phospholipids of patients with atopic dermatitis. Allergy 47:517-521, 1992.
5. Sch fer L, Kragballe K: Abnormalities in epidermal lipid metabolism in patients with atopic dermatitis. J Invest Dermatol 96:10-15, 1991.
6. Hanifin KM, Rajka G: Diagnostic features of atopic dermatitis. Acta Derm Venerol (suppl) 92:44-47, 1980.
7. Tagami H: Measurement of electrical conductance and impedance. In Serup J, Jemec JBE (eds): Non-Invasive Methods and the Skin. CRC Press, Boca Raton, 1995, pp 159-164.
8. Barel AO, Clarys P: Measurements of epidermal capacitance. In Serup J, Jemec JBE, (eds): Non-Invasive Methods and the Skin. CRC Press, Boca Raton, 1995, pp 165-172.
9. Barel AO, Clarys P: Comparison of methods for measurement of transepidermal water loss. In Serup J, Jemec JBE (eds): Non-Invasive Methods and the Skin. CRC Press, Boca Raton, 1995, pp 179-184.
10. Zlotogorski A: Measurement of skin surface pH. In Serup J, Jemec JBE (eds): Non-Invasive Methods and the Skin. CRC Press, Boca Raton, 1995, pp 223-228.
11. Melnik B, Plewig G: Atopic dermatitis and disturbances of essential fatty acid and prostaglandin E metabolism. J Am Acad Dermatol 25:859-860, 1991.
12. Melnik BC, Plewig G: Is the origin of atopy linked to deficient conversion of omega-6-fatty acids to prostaglandin E1? J Am Acad Dermatol 21:557-563, 1989.
13. Melnik BC, Plewig G, Tschung T: Disturbances of essential fatty acid and prostaglandin E-mediated immunoregulation in atopy. Prostaglandins Leukot Essent Fatty Acids 42:125-130, 1991.
14. Sch fer L, Kragballe K: Supplementation with

evening primrose oil in atopic dermatitis: effect on fatty acids in neutrophils and epidermis. Lipids 26:557-560, 1991.
15. Morse PF, Horrobin DF, Manku MS, et al.: Meta-analysis of placebo-controlled studies of the efficacy of Epogam in the treatment of atopic eczema. Relationship between plasma essential fatty acid changes and clinical response. Br J Dermatol 121;75-90, 1989.
16. Bordoni A, Biagi PL, Masi M, et al.: Evening primrose oil (Efamol) in the treatment of children with atopic eczema. Drugs Exp Clin Res 14:291-297, 1988.
17. Bordoni A, Biagi PL, Masi M, et al.: A long-term study on the use of evening primrose oil (Efamol) in atopic children. Drugs Exp Clin Res 14:285-290, 1988.
18. Werner Y, Lindberg M: Transepidermal water loss in dry and clinically normal skin in patients with atopic dermatitis. Acta Derm Venereol 65:102-105, 1985.
19. Werner Y: The water content of the stratum corneum in patients with atopic dermatitis. Measurement with the Corneometer CM 420. Acta Derm Venereol 66:281-284, 1986
20. Di Nardo A, Wertz P, Giannetti A, Seidenari S: Ceramide and cholesterol composition of the skin of patients with atopic dermatitis. Acta Derm Venereol 78:27-30, 1998.