THE EFFECT OF PUVA ON ARACHIDONIC ACID METABOLISM IN PSORIASIS

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SUMMARY: Increased prostaglandin E2 and leukotriene B4 levels have important roles in the pathogenesis of psoriasis. Ten patients with psoriasis vulgaris undergoing psoralen+UVA (PUVA) treatment were studied. Prostaglandin E2-like activity (PGE2-LA) and leukotriene B4-like activity (LTB4-LA) were determined in the lesional and healing skin before and during PUVA treatment. When compared with the pretreatment levels, LTB4-LA was found to be significantly decreased after treatment. There was no statistically significant difference in PGE2-LA before and during treatment. We conclude that PUVA may be effective in the treatment of psoriasis by acting on lipooxygenase pathway providing a decrease in leukotriene B4 levels.

Key Words: Eicosanoids, Photochemotherapy, Psoriatic Lesion.

INTRODUCTION

Psoriasis vulgaris is a common chronic inflammatory disease. In recent years, the changes in arachidonic acid (AA) metabolism have been found to be one of the factors responsible in the pathogenesis of psoriasis (3, 5, 9, 18). The increase in levels of free AA in psoriatic skin was first demonstrated in 1975 (7).

Successive studies have demonstrated that the increase in levels of lipooxygenase (LO) pathway products like 12-HETE and leukotriene B4 (LTB4) have been greater than the increase in cyclooxygenase (CO) pathway products like prostaglandin E2 (PGE2). Duell et al. have reported LTB4 and 12-HETE levels to be 7-11 times higher in the involved and 3-7 times higher in the uninvolved skin of psoriatic patients compared with those of the normal skin (7, 24).

LTB4 causes the characteristic histopathologic findings of early psoriasis like intraepidermal microabscess formation or keratinocyte proliferation in minute amounts when injected to the normal skin intradermally or subcutaneously (6, 16, 20).

Psoralen + UVA (PUVA) is successful in the treatment of psoriasis. The precise action mechanism of PUVA in the treatment of psoriasis is not known. The inhibitory effect of PUVA on edema and inflammation caused by AA in the skin have been shown in animal models (5).

We compared the LTB4 and PGE2-like activities (LA) by bioassay method in the involved skin before PUVA treatment and healed skin after PUVA treatment in chronic plaque type psoriasis patients.
MATERIALS AND METHODS

The study was carried out in ten patients with generalized plaque type psoriasis who underwent PUVA treatment. There were four men and six women. Their ages were between 18 to 68 years with a mean age of 41.3 years. At the time of the study, they were diagnosed as having psoriasis for one to 13 years with a mean disease period of 6.4 years. The cases were selected among patients receiving no local or systemic drug treatments for the last fifteen days (Table 1).

<table>
<thead>
<tr>
<th>Number</th>
<th>Name</th>
<th>Sex</th>
<th>Age</th>
<th>Clinical appearance of the lesions</th>
<th>Disease period</th>
<th>Total UVA dose (J/cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M.A.</td>
<td>M</td>
<td>68</td>
<td>Widespread plaque type</td>
<td>13 years</td>
<td>76</td>
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<td>2</td>
<td>F.T.</td>
<td>F</td>
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<tr>
<td>3</td>
<td>M.P.</td>
<td>F</td>
<td>18</td>
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<td>165</td>
</tr>
<tr>
<td>4</td>
<td>M.E.</td>
<td>F</td>
<td>18</td>
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<td>1.5 years</td>
<td>141.5</td>
</tr>
<tr>
<td>5</td>
<td>A.B.</td>
<td>M</td>
<td>23</td>
<td>Widespread plaque type</td>
<td>4 years</td>
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<tr>
<td>6</td>
<td>P.O.</td>
<td>F</td>
<td>44</td>
<td>Widespread plaque type</td>
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<td>36.5</td>
</tr>
<tr>
<td>7</td>
<td>A.Y.</td>
<td>M</td>
<td>60</td>
<td>Widespread plaque type</td>
<td>10 years</td>
<td>96</td>
</tr>
<tr>
<td>8</td>
<td>Y.K.</td>
<td>M</td>
<td>68</td>
<td>Widespread plaque type</td>
<td>1 years</td>
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</tr>
<tr>
<td>9</td>
<td>M.C.</td>
<td>F</td>
<td>28</td>
<td>Widespread plaque type</td>
<td>10 years</td>
<td>97.5</td>
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<tr>
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<td>N.B.</td>
<td>F</td>
<td>25</td>
<td>Widespread plaque type</td>
<td>7 years</td>
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</tr>
</tbody>
</table>

Table 1: Clinical features of the patients.

Skin biopsies with a thickness of 3-4 mm were performed from the lesional skin of all patients. Two hours after the administration of oral 8-methoxypsoralen (0.6 mg/kg/day) UVA treatment was begun with a dose of 0.5 J/cm². PUVA was applied twice a week to all patients. The dose of UVA were adjusted for each patient and a 0.5 J/cm² increase were made in every session according to the clinical condition of the patients. Lesions showed improvement starting from a total dose of 36.5 J/cm² to 165 J/cm² with a mean dose of 98.6 J/cm². Following the treatment period, another biopsy was taken from the cleared skin near the first biopsy site. The specimens were stored in -20°C until they were studied.

PGE2-LA was determined by tissue specimens for 15 minutes at 3000 cps at +40°C after homogenizing with 1 N HCl, chemical sea sand and adding 2 ml of ethyl acetate. The ethyl acetate phase was then separated and evaporated with nitrogen gas.

Rat stomach fundic muscle was used for PGE2-LA determinations (13). Fundic muscle properly prepared was superfused at constant current with Krebs solution which had been heated to 37°C and aerated with 5% CO₂ and 95% O₂. After getting a standard dose response curve, 1 ml Krebs solution was added to the specimens and thoroughly shaken. 0.1 ml of that solution was applied to the smooth muscle. The contractions observed were compared with the standard dose response curve.

In order to determine LTB4-LA, the specimens were homogenized with 1 N HCl, chemical sea sand and 4 mg/g acetyl salicylic acid after weighing. The homogenate was centrifuged for 15 minutes at 3000 cps at +40°C following the addition of 2 ml ethyl acetate. Afterwards the ethyl acetate phase was separated and evaporated with nitrogen gas.

Guinea pig ileum was used for LTB4-LA determinations as described by Sanhuan (21). The procedure used for PGE2-LA determinations was applied again.

Isotonic recordings were magnified twelve times and plotted on a kymograph. Statistical analysis was made by using the Student’s t test.

RESULTS

The mean LTB4-LA before PUVA treatment in psoriatic patients was 5.090 ± 1.726 ng/g. LTB4-LA mean value was decreased in all cases after
PUVA treatment to 2.130 ± 1.079 ng/g. This decrease was statistically significant (P<0.05). PGE2-LA before treatment had a mean value of 3.860 ± 2.728 ng/g. After PUVA treatment PGE2-LA was decreased in six patients, increased in three patients and was the same in one patient. The mean PGE2-LA during treatment was 1.960 ± 1.595 ng/g. This decrease in mean values was not statistically significant (Table 2).

<table>
<thead>
<tr>
<th>Number</th>
<th>Name</th>
<th>LTB4-LA ng/g</th>
<th>PGE2-LA ng/g</th>
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<td></td>
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<td>A.T.</td>
</tr>
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<td>1.8</td>
</tr>
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<td>2.2</td>
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<tr>
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<td>M.P.</td>
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<td>1.8</td>
</tr>
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<td>2.1</td>
</tr>
<tr>
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<td>A.Y.</td>
<td>6.2</td>
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</tr>
<tr>
<td>8</td>
<td>Y.K.</td>
<td>5.5</td>
<td>1.8</td>
</tr>
<tr>
<td>9</td>
<td>M.C.</td>
<td>4.8</td>
<td>4.8</td>
</tr>
<tr>
<td>10</td>
<td>N.B.</td>
<td>4.6</td>
<td>2.4</td>
</tr>
</tbody>
</table>

Table 2: LTB4-LA and PGE2-LA values before and after PUVA treatment.

DISCUSSION

AA is the precursor of the biologically active substances named eicosanoids. AA is released from the cell membrane phospholipids by the activation of the enzyme phospholipase A2 with a variety of mechanical, chemical and immunological stimuli (23).

The metabolism of AA increases in psoriatic skin (3, 5, 9, 15, 18, 19, 24). Increased levels of 12-HETE, LTB4 and PGE2 in psoriatic skin are responsible for the characteristic findings like microabscesses, increased epidermal turnover and abnormal cellular differentiation. Increased LTB4 is a potent chemotactic factor especially for polymorphonuclear leukocytes. Intraepidermal microabscess formation containing polymorphonuclear leukocytes was reported after minute amounts of intradermal or subcutaneous LTB4 injection (1, 2, 6, 16, 17, 19, 22).

Another effect of LTB4 is to increase the proliferation of keratinocytes by stimulating the DNA synthesis in keratinocyte cultures (3, 10, 15). PGE2 is responsible for the increase of proliferation, vasodilation, erythema and to a lesser extent for chemotaxis (20).

The increase in AA metabolism commences by the activation of phospholipase A2 in psoriatic skin. The increase in the products of lipoxygenase pathway like 12-HETE and LTB4 is more pronounced than the increase in the products of cyclooxygenase pathway like PGE2 and PGF2. These findings suggest that there is an endogenous inhibitor of CO pathway in psoriatic skin which causes a shift to LO pathway in AA metabolism (3). Ellis et al. (8) observed an increase in psoriatic lesions after topical application of indomethacin: an inhibitor of CO pathway. Conversely an improvement in lesions was observed after applying benoxaprofen which is an inhibitor of LO pathway. Thus the inhibition of CO pathway alone is not sufficient whereas the inhibition of LO pathway is effective in the treatment of psoriasis (2, 15).

The action mechanism of PUVA which is used effectively in psoriasis is not completely understood. However, it is known that it affects AA metabolism (18). Danno et al. showed that erythema and edema produced by topical application of AA on rat ear disappeared by topical psoralen and UVA treatment; but neither psoralen nor UVA in normal doses had an effect in AA metabolism (5). Chang et al. also observed that polymorphonuclear leukocyte migration produced by topical LTB4 was inhibited after UVB or PUVA. They proposed that UV waves could induce the release of some eicosanoids which decreased the effect of LTB4 (4). It is also known that UVA increases the levels of PGE2 in normal skin (12). Although it can be concluded that PUVA treatment is effective in psoriatic patients by increasing the synthesis of PGE2, there are studies showing that PUVA has no effect on PGE2 levels (11, 14).

Consistent with these studies we could find no statistically significant difference in PGE2-LA in psoriatic skin before or after PUVA treatment. However, PUVA induced a significant decrease in LTB4-LA. One of the mechanisms of action of PUVA in the treatment of psoriasis is to decrease the LTB4 levels by acting on LO pathway. There is no significant difference in PGE2 levels during PUVA treatment. This suggests that PUVA is effective in healing the psoriatic lesions without
much change in PGE2 levels while causing decrease in LTB4 levels.

In conclusion, the action of PUVA on LTb4 levels has an important role in the treatment of psoriasis. It can be hypothesized as one of its action mechanisms in the treatment of this disease. However, further studies are necessary to further clarify the issue.

REFERENCES


