

PROSTAGLANDINS IN PUVA-TREATED PSORIASIS

Helen Heiligstätt, Vibeke Kassis, Kaare Weismann
and Jørgen Søndergaard

*Departments of Dermatology, University of Copenhagen, Rigshospital
and Hvidovre Hospital, Copenhagen, Denmark*

Abstract. The biosynthesis of prostaglandins (PG) in biopsies from 9 patients with recalcitrant psoriasis was studied before, during, and after treatment with 8-methoxy-psoralen and long-wave ultraviolet light (UVA). No statistical difference was found between the results obtained before, during, and after the treatment. In PGE_1 -equivalents, the concentration in involved psoriatic skin was 2.16 ± 0.31 ng (mean $\pm$ S.E.M.) before, 2.01 ± 0.33 ng during, and 2.85 ± 0.31 ng per g wet weight after PUVA. In uninvolved skin the concentrations were 2.38 ± 0.26 ng, 2.23 ± 0.15 ng and 3.29 ± 0.24 ng per g wet weight, respectively. In the presence of exogenous arachidonic acid in the incubation medium the activity formed was higher, but no statistical difference was found between pretreatment values and those obtained during and after PUVA treatment. The hypothesis that PUVA treatment stimulates PG biosynthesis, thus accounting for the beneficial therapeutic antipsoriatic effect, could not be confirmed.

Key words: Prostaglandins; Biosynthesis; PUVA; Psoriasis

The role of prostaglandins (PG) in several inflammatory skin disorders is now widely accepted. These include primary irritant dermatitis (19), allergic contact dermatitis (13) and inflammation due to ultraviolet (UV) irradiation (5, 18). In these conditions PG synthesis is increased. By contrast, it is low in psoriasis (2, 15). A decreased stimulation of the cyclic nucleotide system by PG's, causing an imbalance in the ratio of cAMP to cGMP, might be relevant to altered epidermal cell function in psoriasis.

It is conceivable that treatment with 8-methoxy-psoralen and long-wave ultraviolet light, PUVA treatment stimulates PG biosynthesis and thus, to some extent, might account for the beneficial results, possibly influencing cyclic nucleotide concentrations and mitotic activity.

In order to test this hypothesis we analysed skin biopsies from patients with psoriasis before, during, and after PUVA treatment.

MATERIAL AND METHODS

Patients

Nine patients (4 female and 5 male patients) with widespread recalcitrant psoriasis were studied. Each patient was treated perorally with 8-methoxy-psoralen (Meladinine®, The Memphis Chemical Co., Cairo, Egypt) 2 hours prior to UVA exposure. The dose was approximately 0.5 mg 8-methoxy-psoralen per kg body weight. The UVA source consisted of 48 tube lamps (Philips TL/08) with a spectral range of 320-400 nm. The light energy reaching the body surface at a distance of 25-30 cm was about 4.5 Joule/cm². PUVA therapy was administered three times a week according to a fixed schedule, starting with 1.4 Joule/cm² and increasing by 0.5 Joule/cm² at the subsequent exposures up to a maximum of 4.2 Joule/cm². This procedure has proved effective in the treatment of refractory psoriasis (21).

Sampling

Before PUVA therapy, punch biopsies, 6 mm in diameter, were taken from involved and uninvolved skin on the lateral aspect of the thighs of each patient. In 5 patients, additional biopsies were taken 9 to 10 days after the start of treatment when they had received about 12 Joule/cm². In 4 patients the second set of biopsies was taken when their psoriasis had cleared, after a total dose of 30-75 Joule/cm² which was given over 25-50 days. The skin specimens were immediately frozen in liquid nitrogen and, if not analysed the same day, stored for up to one week at -20°C.

Reagents

The standard PG's were a gift from Professor D. A. van Dorp and Dr P. F. Wilde of Unilever Research Laboratories. ³H-labelled PGE_1 was obtained from New England Nuclear Corp. and had a specific activity of 110 Ci/mmol. ³H-labelled 5,8,11,14-eicosatetraenoic acid (arachidonic acid) with a specific activity of 80 Ci/mmol was supplied by New England Nuclear Corp.

Table I. Biosynthesis of prostaglandins from endogenous precursors in skin of patients with psoriasis treated with PUVA

Patient	Before	During	After
<i>Involved skin</i>			
1	1.93		2.72
2	2.66		2.52
3	3.82		3.76
4	2.49		2.40
Mean±			
S.E.M.	2.73±0.40		2.85±0.31
5	1.89	1.82	
6	2.14	2.37	
7	3.21	3.10	
8	1.29	1.56	
9	2.25	1.20	
Mean±			
S.E.M.	2.16±0.31	2.01±0.33	
<i>Uninvolved skin</i>			
1	1.96		3.38
2	2.62		3.30
3	4.45		3.82
4	4.04		2.64
Mean±			
S.E.M.	3.27±0.59		3.29±0.24
5	1.82	2.44	
6	3.18	1.73	
7	2.71	2.64	
8	1.89	2.23	
9	2.28	2.10	
Mean±			
S.E.M.	2.38±0.26	2.23±0.15	

Table II. Biosynthesis of prostaglandins from exogenous arachidonic acid in skin of patients with psoriasis treated with PUVA

Patient	Before	During	After
<i>Involved skin</i>			
1	6.25		5.85
2	2.92		3.92
3	5.62		7.90
4	6.06		5.67
Mean±			
S.E.M.	5.21±0.78		5.84±0.81
5	2.37	2.95	
6	4.56	4.44	
7	3.38	4.47	
8	3.45	2.50	
9	5.07	3.41	
Mean±			
S.E.M.	3.77±0.48	3.55±0.40	
<i>Uninvolved skin</i>			
1	8.61		9.18
2	3.67		4.78
3	4.89		4.21
4	8.33		5.44
Mean±			
S.E.M.	6.38±1.24		5.90±1.12
5	3.24	4.22	
6	4.24	3.23	
7	4.75	4.69	
8	4.85	5.96	
9	6.07	8.41	
Mean±			
S.E.M.	4.63±0.46	5.30±0.89	

Biosynthesis from endogenous precursor acids and from labelled arachidonic acid

The methods used were adopted from Jonsson & Änggård (12) as described previously (14). The punch biopsy was homogenized in a glass homogenizer in 10 ml medium (0.15 mol/l potassium phosphate buffer, pH 7.4, containing reduced glutathione 1.5 mmol/l and EDTA 30 mmol/l). Five ml of this homogenate was used for the study of the biosynthesis from endogenous precursor acids, while the remaining 5 ml was used for determination of the biosynthesis after addition of labelled arachidonic acid. The subsequent extraction procedures were identical with those described by Jonsson & Änggård (12).

After column chromatography on 0.5 g of silicic acid, further separation of PG was carried out as suggested by Horton (11) and previously described by Greaves et al. (8) using thin-layer silica gel G plates and co-chromatography with PG standards in the A1 solvent system, described by Gréen & Samuelsson (9).

Bioassay

Bioassay was performed on eluates reconstituted in DeJalon's solution using the striated part of the ascending

colon of gerbil and on rat stomach strip, as described by Weeks et al. (20). Three-point assays were done. The results were expressed in PGE₁-equivalents.

RESULTS

PUVA-treatment caused erythema in all patients during the first week, and this was gradually replaced by an even hyperpigmentation. In 6 patients (nos. 1, 2, 3, 5, 6 and 7, Table I) psoriasis cleared completely during therapy and in the remaining patients 75–80% was cleared.

The biosynthesis of PG in the biopsies from the psoriatic skin taken before, during, and after PUVA treatment was determined biologically using gerbil colon and rat stomach strip after incubation for 20 min at 37°C. Without addition of arachidonic acid to the incubation medium, the concentration in the involved skin in PGE₁-equivalents (mean ± S.E.M.)

was $2.73/2.16 \pm 0.40/0.31$ ng/g wet weight, 2.01 ± 0.33 ng/g wet weight and 2.85 ± 0.31 ng/g wet weight before, during and after PUVA treatment, respectively. The values during and after PUVA treatment do not differ statistically from those obtained before treatment (Table I). The corresponding values from uninvolved skin were $3.27/2.38 \pm 0.59/0.26$ ng/g wet weight before, 2.23 ± 0.15 ng/g wet weight during and 3.29 ± 0.24 ng/g wet weight after PUVA treatment (Table I). These values were not statistically different ($p > 0.05$).

In the presence of exogenous arachidonic acid in the incubation medium an increased capacity to synthesize PG was found in all skin specimens (Table II). However, the increased capacity to synthesize PG was of the same order of magnitude in biopsies obtained during and after PUVA treatment, as compared with untreated, uninvolved and involved psoriatic skin ($p > 0.05$).

After the column chromatography, further attempts to characterize the activity formed during the incubation period in the presence of exogenous arachidonic acid were made, using thin-layer chromatography. In the AI solvent system (9) 95% of the total pharmacological activity co-chromatographed with PGE₁ and the remainder, about 5%, with PGF. No difference was found in the ratio E/F PG by thin-layer chromatography of activity originating from involved and uninvolved psoriatic skin during and after PUVA, as compared with pretreatment activity.

DISCUSSION

The present results have clearly shown that PUVA treatment did not influence PG synthesis in psoriatic skin. Thus, no increase in the rate of synthesis occurred during PUVA treatment, when the inflammatory erythema was clinically evident. By the end of the treatment period, when the inflammatory changes had subsided and the psoriatic lesions almost healed, the values for PG synthesis were found to be slightly higher, though they did not differ significantly from those obtained during or before the treatment.

PUVA treatment caused a phototoxic inflammatory erythema in the skin, and as it has been found in several other inflammatory conditions (1, 4, 6, 8, 14, 19), one might have expected that PG synthesis would be increased. UVB treatment is known to increase rat skin PG levels several fold (5), and in

normal human skin exposed to UVB light, PG-like compounds were detected in increased concentrations 24 hours after irradiation (7, 18). The unexpectedly low rate of PG synthesis found in this study might have been due to the presence of a PG-synthesis inhibitor in the psoriatic lesions, although as yet we have no data to substantiate this suggestion. Penneys et al. (17) recently showed evidence of a PG inhibitor in UV-treated psoriatic plaques. Consequently, the beneficial therapeutic effect of PUVA treatment might still be related to an increased PG synthesis which, however, is masked by an inhibitor in the plaques. The unchanged synthesis in the uninvolved skin renders this possibility less likely, however.

Alternatively, the effect of PUVA on psoriasis may not implicate the PG synthesis at all. However, several investigations have indicated that UV radiation does in fact increase PG biosynthesis. Thus, Gandhi et al. (5) found elevated levels of PG's after UVB treatment of rat skin. Indirect evidence for the involvement of PG's in UV inflammation was furthermore presented by Eaglestein et al. (3) and Hensby et al. (10). UVB radiation was used in their experiments, and the inflammatory responses were inhibited by PG synthesis inhibitors. By contrast, erythema induced by UVA was recently found not to be inhibited by indomethacin (16), an observation which provides indirect evidence that PG's are not involved as mediators of UVA erythema.

Finally, a disturbed balance between E and F PG causing alterations in the intracellular ratio of cyclic AMP to cyclic GMP might explain part of the beneficial effect of PUVA on psoriasis. This, however, was not supported by our findings, as we were unable to detect any change in the ratio between PGE and PGF during and after PUVA therapy.

ACKNOWLEDGEMENT

This work was supported by grant 512-1086 from the Danish State Research Foundation.

REFERENCES

1. Arturson, G., Hamberg, M. & Jonsson, C.-E.: Prostaglandins in human burn blisters fluid. *Acta Physiol Scand* 87: 270, 1973.
2. Aso, K., Deneau, G., Krulig, L., Wilkinson, D. I. & Farber, E. M.: Epidermal synthesis of prostaglandins and their effect on levels of cyclic adenosine 3',5'-monophosphate. *J Invest Dermatol* 64: 326, 1975.
3. Eaglestein, W. & Marsico, A.: Dichotomy in response

- to indomethacin in UV-C and UV-B induced ultraviolet light inflammation. *J Invest Dermatol* 65: 238, 1975.
4. Förström, L., Haapalahti, J. & Suramo, M.-L.: Prostaglandin E in blistering skin diseases. *Acta Dermatovener (Stockholm)* 56: 495, 1976.
 5. Gandhi, V. M. & Mathur, G. P.: Prostaglandin activity in human and albino rat skin. *J Invest Dermatol* 58: 291, 1972.
 6. Goldyne, M. E., Winkelmann, R. K. & Ryan, R. J.: Prostaglandin activity in human cutaneous inflammation: Detection by radioimmunoassay. *Prostaglandins* 4: 737, 1973.
 7. Greaves, M. W. & Søndergaard, J.: Pharmacologic agents released in ultraviolet inflammation studied by continuous skin perfusion. *J Invest Dermatol* 54: 365, 1970.
 8. Greaves, M. W., Søndergaard, J. & McDonald-Gibson, W.: Recovery of prostaglandins in human cutaneous inflammation. *Br Med J* 258: 258, 1971.
 9. Gréen, K. & Samuelsson, B.: Prostaglandins and related factors. XIX. Thin-layer chromatography of prostaglandins. *J Lipid Res* 5: 117, 1964.
 10. Hensby, C. N., Plummer, N. A., Camp, R. D., Kobza Black, A. & Greaves, M. W.: UVB erythema in human skin: Inconsistent correlation with prostaglandin and arachidonate activity. ESDR-meeting, Amsterdam, May, 1977.
 11. Horton, E. W.: *Recent Advances in Pharmacology*, 4th ed. J. & A. Churchill Ltd., London, 1968.
 12. Jonsson, C.-E. & Ånggård, E.: Biosynthesis and metabolism of prostaglandin E_2 in human skin. *Scand J Clin Lab Invest* 29: 289, 1972.
 13. Jørgensen, H. P. & Søndergaard, J.: Biosynthesis of prostaglandins in human allergic contact dermatitis. *Arch Derm Res* 257: 143, 1976.
 14. Jørgensen, H. P. & Søndergaard, J.: Biosynthesis of prostaglandins by human inflamed skin. *Acta Dermatovener (Stockholm)* 56: 11, 1976.
 15. Kassis, V., Weismann, K., Heiligstätt, H. & Søndergaard, J.: Synthesis of prostaglandins by psoriatic skin. *Arch Derm Res* 259: 207, 1977.
 16. Morison, W. L., Poul, B. S. & Parrish, J. A.: The effects of indomethacin on long-wave ultraviolet-induced delayed erythema. *J Invest Dermatol* 68: 130, 1977.
 17. Penneys, N. S., Ziboh, V. A., Simon, P. & Lord, J. P.: Pathogenesis of Woronoff's Ring in psoriasis. *Arch Dermatol* 112: 955, 1976.
 18. Søndergaard, J. & Greaves, M. W.: Pharmacological studies in inflammation due to exposure to ultraviolet radiation. *J Pathol* 101: 93, 1970.
 19. Søndergaard, J., Greaves, M. W. & Jørgensen, H. P.: Recovery of prostaglandins in human primary irritant dermatitis. *Arch Dermatol* 110: 556, 1974.
 20. Weeks, J. R., Schultz, J. R. & Brown, W. E.: Evaluation of smooth muscle bioassays for prostaglandins E_1 and $F_{1\alpha}$. *J Appl Physiol* 25: 783, 1968.
 21. Weismann, K., Howitz, J. & Bro-Jørgensen, A.: Treatment of resistant psoriasis with oral 8-methoxypsoralen and longwave ultraviolet light (PUVA). *Acta Dermatovener (Stockholm)* 57: 73, 1977.

Received September 13, 1977

J. Søndergaard, M.D.
Department of Dermatology
Hvidovre Hospital
DK-2650 Hvidovre
Denmark