

INFLUENCE OF ULTRAVIOLET LIGHT ON ITCH AND FLARE REACTIONS IN HUMAN SKIN INDUCED BY HISTAMINE AND THE HISTAMINE LIBERATOR COMPOUND 48/80

Bo Fjellner and Östen Hägermark

Department of Dermatology, Karolinska sjukhuset, Stockholm, Sweden

Abstract. The itch and flare responses induced by intradermal injection of histamine and the histamine liberator compound 48/80 were studied in healthy volunteers before and after exposure to UVB, UVA or PUVA administered 2-3 times weekly for 4 weeks. All three modalities were found to inhibit the responses induced by compound 48/80. The degree of tanning was most pronounced after PUVA and weakest after UVB, without any correlation between tanning and inhibition of itch. In contrast, when induced by histamine, the responses were not inhibited to the same extent, pronounced and significant inhibition being observed only for itching in subjects exposed to UVB. It is concluded that UVB, UVA and PUVA all might be of benefit in treating pruritic states if histamine release is involved and that UVB might have an additional effect by inducing hyposensitivity to itching stimuli.

According to clinical experience, pruritic dermatoses, e.g. atopic dermatitis, often improve when the skin is exposed to ultraviolet light. Under controlled conditions beneficial results have been observed in treating uremic pruritus with UVB (5, 6, 7, 16, 17), or UVA (10) and disseminated neurodermatitis, nodular prurigo and urticaria pigmentosa with PUVA (1, 8, 11, 21). Consistent with these observations, we had noted that itch and flare responses to intradermal injection of histamine and the histamine liberator compound 48/80 seemed to be decreased in suntanned skin. In the present paper this preliminary observation was studied further in volunteers exposed to UVB, UVA or PUVA 2 hours after oral 8-methoxypsoralen administration (PUVA).

MATERIAL AND METHODS

Subjects

Twenty-nine healthy volunteers, 9 men and 20 women, median age 33 (range 21-50) years, were enrolled in this study. Each subject took part in only one of three experimental series, except for one person who participated in two of the experiments. All subjects belonged to skin type

III, i.e. following sun exposure their skin sometimes got burned and always tanned (14). None of the subjects obtained any oral or topical drug during the test period.

Light sources

UVB and UVA irradiations were given in Waldmann light cabins "UVB 1000" and "UVA 1000" (H. Waldmann GmbH + Co, Werk für Lichttechnik, Villingen-Schwenningen, W. Germany). The UVB radiation unit had 26 Sylvania lamps (UV6) emitting a continuous spectrum of approximately 295-350 nm with intensity maximum at 310 nm. The average minimum erythema dosage (MED) for this equipment was about 3 min for skin type III. The UVA radiation unit was equipped with 28 Sylvania UVA fluorescent lamps emitting a continuous spectrum of approximately 320-400 nm with intensity maximum at 365 nm. Both UVB and UVA lamps were 180 cm long. For details concerning spectral irradiances and light intensities, see ref. 3.

Treatment procedure

The whole body, except for the left upper arm which was covered by a cloth, was exposed to UVB or UVA light two to three times weekly for a period of 4 weeks. In a third experiment UVA light was administered in the same way but 2 hours after previous oral intake of 8-methoxypsoralen (8-MOP) tablets (for dosages, see Table 1), so-called PUVA regimen. The plasma level of 8-MOP 2 hours after oral intake was 147 ± 28 ng/ml (mean \pm SEM). The quantitative determination of 8-MOP was carried out by gas chromatography with selected ion monitoring using $^2\text{H}_3$ -labelled 8-MOP as an internal standard. The mass spectrometer was focused at m/z : 216 (M^+) and 219. The eyes were protected by dark glasses during the exposures. The dosage of UVA in the PUVA regimen and of UVB

Table 1. Dose regimen for 8-methoxypsoralen in PUVA therapy

Body weight (kg)	Dosage of 8-methoxypsoralen (mg)
< 50	20
51-65	30
66-80	40
> 80	50

Table II. Itch and flare responses after 4 weeks of UV treatment (mean \pm S.E.M.). Ten healthy volunteers in each UV series

Treatment procedure	Liberating agent			
	Histamine		Compound 48/80	
	Itch (sec)	Flare (mm ²)	Itch (sec)	Flare (mm ²)
UVB				
Pre-irradiation value	120.4 \pm 21.1	963.0 \pm 136.4	174.0 \pm 42.4	992.6 \pm 163.7
Light exposed skin	51.4 \pm 12.2	893.6 \pm 105.0	66.9 \pm 14.0	650.4 \pm 69.4
Light protected skin	75.7 \pm 9.2	821.0 \pm 114.2	115.7 \pm 22.2	905.6 \pm 150.2
UVA				
Pre-irradiation value	107.2 \pm 21.1	835.5 \pm 72.6	116.6 \pm 27.4	817.2 \pm 53.2
Light exposed skin	84.0 \pm 31.6	775.3 \pm 63.7	72.4 \pm 20.0	567.4 \pm 55.1
Light protected skin	132.5 \pm 32.0	737.7 \pm 39.8	103.1 \pm 21.9	783.0 \pm 59.2
PUVA				
Pre-irradiation value	108.9 \pm 23.4	1 042.8 \pm 108.1	124.0 \pm 26.9	927.5 \pm 136.4
Light exposed skin	81.9 \pm 18.7	819.7 \pm 82.3	53.4 \pm 10.9	667.0 \pm 97.1
Light protected skin	90.4 \pm 20.6	776.7 \pm 74.5	81.2 \pm 15.6	809.8 \pm 87.3

were individually adjusted and increased as rapidly as possible to induce erythema and pigmentation. The highest UVB doses attained ranged from 1.2 to 2.1 J/cm² and for UVA in the PUVA regimen from 8 to 14 J/cm². In the UVA experiment a constant dose of 15 J/cm² per irradiation was used. The total number of exposures were: UVB 11–12, UVA 9–12 and PUVA 8–12. The total UV doses (mean \pm SEM) were for UVB 10.9 \pm 0.8 J/cm², for UVA 166.0 \pm 4.2 J/cm² and for UVA in the PUVA regimen 74.6 \pm 7.9 J/cm².

Intradermal tests

The cutaneous responses to 0.01 ml of intradermally injected histamine and compound 48/80 were observed before and after the series of UV exposures. The intradermal tests were performed about 48 hours after the last UV exposure. The solution studied were injected in the lateral aspect of the upper arms. The duration of the itch response was recorded. The area of the flare reaction was measured with a planimeter (model 317 from Gebrüder Haff GmbH, Pfronten, W. Germany) 5 min after the injections (2).

The substances were dissolved in physiological saline containing 10% (v/v) Sörensen phosphate buffer (Na₂HPO₄+KH₂PO₄, 67 mM), pH 7.4. The solutions were passed through a Millipore filter (Miltex TM 0.22 μ m) before use.

Compound 48/80 was a gift from Prof. B. Högberg, Leo AB, Helsingborg, Sweden.

RESULTS

The tanning appearing in the irradiated areas was most pronounced in PUVA-treated subjects and least noticeable in those exposed to UVB.

The cutaneous itch and flare responses evoked

by the histamine liberator compound 48/80 were significantly alleviated in subjects exposed to UVB, UVA and PUVA (Table II, Fig. 1a). The itch response appeared to be somewhat more inhibited in the UVB and PUVA regimen, whereas the flare responses decreased to approximately the same extent after the various procedures. When compound 48/80 was injected in skin which had been protected during irradiation, the itch and flare reactions were not statistically significantly decreased. A similar decrease in responses in UV-irradiated skin was not observed for histamine-evoked reactions (Table II, Fig. 1b). However, in subjects treated with UVB the itching was inhibited in exposed skin and after PUVA the flare was slightly decreased in both irradiated and non-irradiated skin.

DISCUSSION

Repeated exposure of human skin to UVB and UVA, with or without previous psoralen administration was followed by decreased itch and flare responses to the histamine liberating agent compound 48/80. The responses to histamine were pronouncedly inhibited only for itching after UVB exposure.

Tanning seemed to be of no importance, since there was no correlation between extent of inhibition and degree of tanning, the latter being weakest after UVB and more pronounced after UVA.

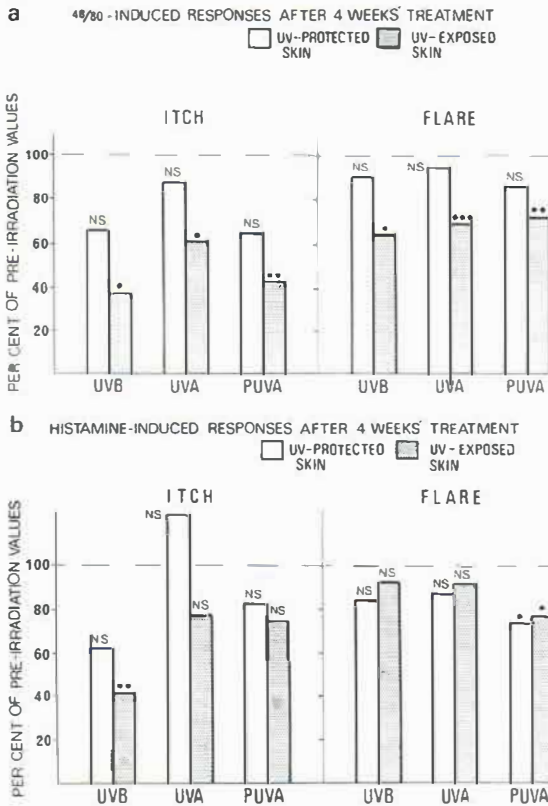


Fig 1 a, b. Itch and flare responses induced by (a) compound 48/80 ($10 \mu\text{g/ml}$), and (b) histamine ($10 \mu\text{g/ml}$) after 4 weeks of UV exposure, 2-3 times a week. The responses are expressed as percentages of the values before irradiation, based on data in Table II. Ten healthy volunteers took part in each UV series. *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$, denote significant inhibition compared with pre-irradiation values (student's *t*-test for paired samples). NS = not significantly influenced.

The results obtained have to be interpreted carefully due to the limited number of volunteers studied. The penetrance of ultraviolet light through human skin may show interindividual differences but in this study each individual served as his/her own control. The radiation sources utilized emit both UVA and UVB light (3). Thus, photoaugmentative mechanisms may also be responsible for the effects observed.

The reduction of compound 48/80-induced responses, but as a rule not to those evoked by histamine, might be explained by an UV-induced inhibition of mast cell release mechanism. This is supported by the *in vitro* finding that histamine release induced by compound 48/80 is inhibited from rat peritoneal mast cells pre-exposed to UVB

or UVA light from the same radiation cabins as used in the present study. The inhibitory effect on mast cells seemed to be exerted primarily by light in the wavelength region of UVB emitted by both cabins (3).

A second explanation for the reduced responses to compound 48/80 might be an UV-induced depletion of mast cell histamine content. Thus, sufficiently high dosages of UVB emitted from a xenon high pressure arc lamp seem to induce histamine liberations *per se* from rat peritoneal mast cells *in vitro* probably by damaging mast cell membranes (3). This was not observed for UVA light (3). Histamine-like activity has also been detected in skin perfusate following UVB-exposure of human skin (19). Furthermore, mast cell injury has been observed following UVB irradiation of animal tissue (9). Conflicting *in vivo* results have been published concerning UVA. When used repeatedly to treat patients with urticaria pruritus the number and morphology of mast cells is reported to be unaffected (10). On the other hand, mast cell damage has been observed following irradiation of rat peritoneum for energy doses exceeding those for UVB (9) and following irradiation of human skin in experimental situations (12).

Thirdly: It has recently been shown that successful PUVA treatment of patients with urticaria pigmentosa was accompanied by a gradual decrease in the major histamine metabolite 1-methyl-4-imidazole-acetic acid in urine concomitant with a decreased number of dermal mast cells (8). Since this occurred without signs of degranulation or immediate histamine release, PUVA was suggested to inhibit mast cells proliferation leading to reduction of skin histamine. A decrease in dermal mast cells without signs of degranulation observed in psoriatic patients after PUVA therapy (18) is in agreement with this observation.

Consequently, UV-light may be of benefit in treating dermatoses where histamine release is conceived to be involved in the pathogenesis, e.g. dermatographism (15). However, mast cells need not necessarily be involved in pruritus. It is sufficient to recall the inadequate responses to antihistamine in many pruritic disorders. Moreover, these disorders are often not associated with signs of histamine release, i.e. erythema and whealing.

Our finding that itching evoked by histamine injection was inhibited in UVB irradiated skin may indicate a non-mast cell dependent decreased re-

sponsiveness to pruritic stimuli. One explanation may be offered by the known effect of UV irradiations on nerve fibres. Thus, ultrastructural degeneration has been observed after UV irradiation (13) as well as changes in excitability properties, together with inactivation of the sodium conductance system (4, 20).

In the present study there were no clear signs of a systemic UV inhibition in skin which had been protected from light. Some of the not statistically significant inhibitions observed may nevertheless be due to a systemic effect not statistically visualized, due to the limited number of patients studied. The PUVA-induced small decrease in histamine-elicited flare in light-protected areas remains to be explained.

ACKNOWLEDGEMENTS

We are indebted to H. Ehrsson for determining the plasma levels of 8-MOP. This investigation was supported by grants from the Karolinska Institute, the Swedish Society for Medical Research, the Edvard Welander Foundation, and the Finsen Foundation. The skilful technical assistance of Mrs Halla Bornstein is gratefully acknowledged.

REFERENCES

1. Christophers, E., Hönigsman, H., Wolff, K. & Langer, A.: PUVA-treatment of urticaria pigmentosa. *Br J Dermatol* 98: 701, 1978.
2. Fjellner, B. & Hägermark, Ö.: Studies on pruritogenic and histamine-releasing effects of some putative peptide neurotransmitters. *Acta Dermatovener (Stockholm)* 61: 245, 1981.
3. — Histamine-release from rat peritoneal mast cells exposed to ultraviolet light. *Acta Dermatovener (Stockholm)* 62: 215, 1982.
4. Giese, A. C.: Action of UV radiation on excitability of cells. *In* The Biologic Effects of Ultraviolet Radiation (ed. F. Urbach), pp. 66-67. Pergamon Press, New York 1969.
5. Gilchrest, B. A., Rowe, J. W., Brown, R. S., Steinman, T. I. & Arndt, K. A.: Relief of uremic pruritus with ultraviolet phototherapy. *N Engl J Med* 297: 136, 1977.
6. Gilchrest, B. A.: Ultraviolet phototherapy of uremic pruritus. *Int J Dermatol* 18: 741, 1979.

7. Gilchrest, B. A., Rowe, J. W., Brown, R. S., Steinman, T. I. & Arndt, K. A.: Ultraviolet phototherapy of uremic pruritus. *Ann Int Med* 91: 17, 1979.
8. Granerus, G., Roupe, G. & Swanbeck, G.: Decreased urinary histamine metabolite after successful PUVA treatment of urticaria pigmentosa. *J Invest Dermatol* 76: 1, 1981.
9. Gróf, P. & Kovács, A.: On the mode of action of UV-light. *Acta Physiol Acad Sci Hung Tomus* 32: 35, 1967.
10. Hindson, C., Taylor, A., Martin, A. & Downey, A.: UVA light for relief of uraemic pruritus. *Lancet* i: 215, 1981.
11. Kubanova, A. A.: PUVA-therapy of patients with itching dermatoses. *Sovetskaya Meditsina* 8: 97, 1979.
12. Kumakiri, M., Hashimoto, K. & Willis, I.: Biologic changes due to long-wave ultraviolet irradiation on human skin: ultrastructural study. *J Invest Dermatol* 69: 392, 1977.
13. — Biological changes of human cutaneous nerves caused by ultraviolet irradiation: Ultrastructural study. *Br J Dermatol* 99: 65, 1978.
14. Melski, J. W., Tanenbaum, L., Parrish, J. A., Fitzpatrick, T. B., Bleich, H. I., and 28 participating investigators: Oral methoxalen photochemotherapy for the treatment of psoriasis: A cooperative clinical trial. *J Inv Dermatol* 68: 328, 1977.
15. Rich, W. G.: Dermographia. *Br Med J* 2: 600, 1949.
16. Saltzer, E. I.: Relief from uremic pruritus: A therapeutic approach. *Cutis* 16: 298, 1975.
17. Shultz, B. C. & Roenigk, H. H.: Uremic pruritus treated with ultraviolet light. *JAMA* 243: 1836, 1980.
18. Stuttgart, G., Brinkmann-Raestrupp, I., Haller, L., Kentsch, V. & Schalla, W.: Melanin granula distribution and phagocytosis in psoriasis vulgaris after PUVA therapy. *Arch Dermatol Res* 264: 29, 1979.
19. Søndergaard, J. & Greaves, M. W.: Pharmacological studies in inflammation due to exposure to ultraviolet radiation. *J Pathol* 101: 93, 1970.
20. Weigele, J. B. & Barchi, R. L.: Ultraviolet irradiation produces loss of saxitoxin binding to sodium channels in rat synaptosomes. *J Neurochem* 35: 430, 1980.
21. Väättäinen, N., Hannuksela, M. & Karvonen, J.: Local photochemotherapy in nodular prurigo. *Acta Dermatovener (Stockholm)* 59: 544, 1979.

Received June 16, 1981

B. Fjellner, M.D.
Department of Dermatology
Karolinska Sjukhuset
S-10401 Stockholm
Sweden