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PUVA THERAPY FOR POLYMORPHOUS LIGHT ERUPTIONS: COMPARISON OF SYSTEMIC METHOXSALEN AND TOPICAL TRIOXSALEN REGIMENS AND EVALUATION OF LOCAL PROTECTIVE MECHANISMS

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Abstract. Twenty-six patients with long-standing, recurrent polymorphous light eruptions were treated with psoralen photochemotherapy. Thirteen patients received oral methoxsalen, while 13 were photosensitized by trioxsalen baths. After an average of 20 PUVA exposures, a good or excellent therapeutic result was achieved in 12 of the orally treated and 10 of the topically treated patients. In most of the cases, clinical desensitization lasted throughout the summer season, without further PUVA exposures. When the polymorphic phototest reaction (PPR) was registered 72 h after skin testing with a medium pressure mercury lamp, a remarkable reduction or total abolition of the reaction was seen in tests made on PUVA-exposed skin, as compared with tests made on a comparable skin site, shielded from UVA exposure during the treatments. A concomitant decrease in the erythemal reactivity (MED) of the skin was usually—though not invariably—seen. It is concluded that in addition to including an increase in the shielding properties of stratum corneum, PUVA treatment may induce non-responsiveness in PMLE skin by other, possibly anti-inflammatory or immunological mechanisms.

Key words: Oral PUVA; Bath PUVA; Polymorphous light eruptions; Phototests

The principle of using graded light exposures to desensitize patients suffering from light sensitivity dermatoses is over 40 years old (1), but has only sporadically been referred to since then (13, 16). Recently, however, encouraging reports have been published on the efficacy of psoralen photochemotherapy (PUVA) for the treatment of polymorphous light eruptions (PMLE) (6, 15) and other photoallergic skin eruptions (5, 14). Hitherto published reports, however, have concerned rather small patients series, and the evaluation of the hyposensitizing effect has been based on clinical grounds only.

We now report our experiences from PUVA treatment of 26 patients with chronic PMLE. Oral and topical (bath) applications of psoralen are compared and the clinical results are supplemented with skin phototest data.

PATIENTS AND METHODS

Patients with long-standing polymorphous light eruptions (PMLE) from the University Dermatological Clinics of Turku (13 patients) and Oulu (13 patients) participated in the study, after having given their informed consent. The personal and clinical data of the patients are given in Table 1. The diagnosis of PMLE was based on a typical history and clinical picture as well as skin phototests and blood biochemistry, as detailed in earlier publications from the participating centres (8). The subdivision into different morphological PMLE types was made according to criteria published earlier (10).

All treatments were started during the period September 1979 to March 1980 when the patients were free from symptoms, except for 2 patients with eczematous eruptions who had moderate skin lesions (patients marked with asterisks in Table 1). The Turku patients (patient group A) were treated with oral 8-methoxypsoralen (Puvalen®, Star Ltd., Tampere, Finland) approximately 0.6 mg/kg body weight, 2 hours before irradiation, whereas the Oulu patients (patient group B) were bathed for 10 minutes in a solution of 50 mg of trioxsalen (Fermion Ltd., Helsinki, Finland) in 150 litres of warm water (7). The faces of the bathed patients were trated by applying 0.01 % trioxsalen in an o/w emulsion for the same period of time. At both centres, irradiation of the patients was performed in stand-up cabins (PUVA 22, Airam, Helsinki) equipped with 22 fluorescent tubes emitting mainly in the UVA (320–400 nm) range with an average output of 10 mW/cm^2 at the distance of the skin. In both patient series, the PUVA treatments were initially given on alternative days, three times a week for 3–4 weeks, and thereafter 1–2 times a week. In both series, the starting UVA dose was 0.05 or 0.1 J/cm^2, but due to the greater phototoxicity induced by the trioxsalen baths vis-à-vis oral methoxsalen, the UVA doses were increased to only 0.6 J/mc^2 during bath PUVA therapy, while doses up to 4–7 J/cm^2 were achieved in the majority of the orally treated patients. Table 1 gives the treatment numbers and total UVA doses for the individual patients. After an average of 20 PUVA exposures (Table 1) the treatment was stopped, the patient instructed to try to maintain the acquired skin pigmenta-

Table I. *Patient characteristics, photochemotherapy dosages and clinical results in 26 PUVA-treated PMLE patients*

A = oral medication, B = topical medication. Patients marked with asterisks had skin symptoms at the start of therapy. Excellent clinical result denotes total freedom from clinical sun sensitivity, good indicates limited symptoms after prolonged sun exposure, and moderate denotes partial relief from PMLE symptoms

Patient	Sex	Age	Disease duration (years)	PMLE subtype	Number of PUVA exposures	Total UVA (J/cm²)	Clinical effect
A 1	♂	18	13	Vesicopapular	18	43	Excellent
A 2*	♂	76	2	Eczematous	25	103	Excellent
A 3	♂	44	15	Vesicopapular	32	135	Excellent
A 4	♀	41	11	Vesicopapular	20	33	Excellent
A 5	♂	29	5	Vesicopapular	18	27	Good
A 6	♂	36	10	Vesicopapular	26	54	Good
A 7	♀	25	7	Vesicopapular	22	55	Good
A 8	♂	68	15	Eczematous	28	40	Good
A 9	♂	53	20	Vesicopapular	17	7	Good
A 10	♀	42	20	Vesicopapular	13	12	Good
A 11	♀	27	22	Vesicopapular	24	57	Good
A 12	♀	44	41	Eczematous	20	27	Good
A 13	♂	60	13	Eczematous	42	169	Moderate
B 1	♂	38	6	Vesicopapular	16	5	Excellent
B 2	♀	24	17	Vesicopapular	15	4	Good
B 3	♀	59	23	Vesicopapular	24	6	Good
B 4	♀	34	6	Vesicopapular	17	5	Good
B 5	♂	43	8	Eczematous	16	4	Good
B 6	♀	31	24	Eczematous	17	5	Good
B 7	♀	36	9	Vesicopapular	16	5	Good
B 8	♀	39	10	Vesicopapular	13	3	Good
B 9*	♂	65	12	Eczematous	22	4	Good
B 10	♂	56	17	Vesicopapular	19	7	Good
B 11	♂	37	9	Eczematous	18	6	Moderate
B 12	♂	53	13	Eczematous	21	5	Moderate
B 13	♂	17	11	Eczematous	19	7	Moderate

tion by natural sun exposure, and the clinical benefit of the treatment monitored monthly by interview and clinical examination.

For skin phototests a medium-pressure mercury lamp device was used as described elsewhere (9). The output from the apparatus is mainly in the UVB range, with a moderate UVA component and some UVC contamination (9). Prior to starting PUVA treatment, graded UV exposures were applied to a series of 1 cm² skin areas by irradiating through rectangular holes in light-proof coverpaper attached either to the lateral aspect of one upper arm (Turku patients) or the upper back (Oulu patients). The irradiated sites were inspected 24 h and 72 h later for assessment of the minimal erythemal dose (MED). At 72 h any delayed, polymorphic phototest reaction (PPR) was quantified on a 0–12 scale (11). During the subsequent PUVA treatments, the patient's one upper arm (Turku patients) or one upper half of the back (Oulu patients) was always shielded from the UVA exposures.

After completion of the treatment series, the phototests were repeated, both on a shielded (unpigmented) skin area and a contralateral, PUVA-exposed (pigmented) skin area. The PPR reactions were recorded in the orally medicated patient series only, while most of the patients from both series were subjected to MED recordings the actual numbers of participating patients being indicated in the Figures.

RESULTS

Clinical responses

During the PUVA treatment, 3 out of the 13 topically treated and 8 out of the 13 orally medicated patients experienced a clear-cut flare of a pruritic rash, clinically similar to sun-induced PMLE. The individual UVA dose that precipitated the rash varied from 0.4 to 0.5 J/cm² in the topically treated and from 0.6 to 7 J/cm² in the orally treated patients. In all cases, PUVA treatment could be continued after a short treatment pause and by temporarily lowering the irradiation dose. Most patients acquired a moderately increased skin pigmentation during the therapy, while in only a few cases was a marked (dark brown) pigmentary response induced.

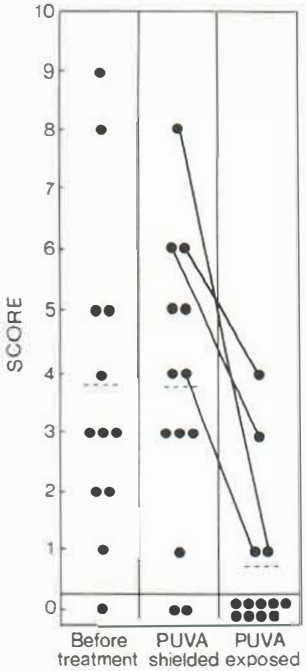

Fig. 1. Comparison of strength of the delayed, polymorphic phototest reaction (PPR) before treatment, in skin shielded during PUVA treatment, and in PUVA-exposed (pigmented) skin in orally medicated PMLE patients.

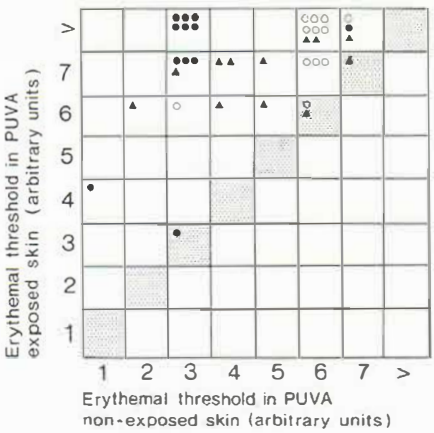

Fig. 2. Minimal erythemal threshold (MED) comparison in PUVA-treated skin site and in skin site shielded from UVA irradiation during treatment sessions. To make the combination of results from two centres possible, the steps of the graded UV exposures are given in arbitrary units, 1–7. The sign > is used to denote lack of reaction to the longest exposure. ○ = 24 h MED, and ● = 74 h MED in orally medicated patients; ▲ = 72 h MED in topically medicated patients.

When the clinical benefit of the therapy was monitored after stopping the PUVA course, a good or excellent clinical photoprotection was found in 12 out of the 13 orally treated and in 10 out of the 13 topically treated cases (Table 1). In most cases, the protection lasted throughout the 4-month summer season, but some patients noticed a diminishing light tolerance in the later summer months. When the threshold tolerance to sun exposure (TTS) achieved after PUVA treatment was compared with that remembered by the patient from previous, unmedicated summers, a protective factor (PF) of at least 12–16 was calculated for patients with excellent clinical response and a protective factor of about 6 for patients with a good clinical response to the treatment.

Skin phototest results

The clinical findings of an increased tolerance to sun exposure was confirmed by the phototest findings. Prior to commencing PUVA treatment, 12 out of the 13 patients to be treated by oral therapy showed a positive PPR, scoring from 1 to 9, mean 3.8 (Fig. 1, left column). After the PUVA course, similar tests made on the upper arm shielded from UVA-irradiation during the PUVA treatments showed no or only a marginal reduction in the PPR, 11 patients reacting positively with scores from 1 to 8, mean 3.7 (Fig. 1, middle column). In contrast, in the tests made on a contralateral, PUVA-exposed skin area, a negative reaction was obtained in 9 patients, while the remaining 4 showed clearly attenuated reactions (Fig. 1, right column).

As the PPR score does not include any evaluation of the erythemal reaction in the test site (11), the minimal erythemal thresholds (MED) were recorded separately and are presented in Fig. 2. On the whole, the MED rose in all recorded cases, except in 2 of the patients treated with oral and 2 treated with topical PUVA (Fig. 2). Despite this, all of these 4 patients had experienced a good clinical photoprotection, and in the 2 orally treated cases the PPR score was diminished (topically treated cases not tested for PPR).

DISCUSSION

This study confirms the beneficial effect of oral photochemotherapy in PMLE, as described in previous, smaller patient series (6, 15). Furthermore, it demonstrates success with topical (bath) PUVA

treatment, previously shown to be useful, e.g. in the treatment of psoriasis (3, 7) and lichen planus (17). As compared with systemic psoralen medication, topical application affords certain practical advantages, including the need for much smaller irradiation periods, i.e. about 1/10 of that for oral therapy (7) and the absence of any need to wear protective goggles except during the irradiation proper.

The present study indicates that the ameliorating effects of PUVA on the light sensitivity in PMLE is due to the action of photoactivated psoralen and not merely to the UVA exposures, as equally good therapeutic results were obtained with the two photochemotherapeutic methods in spite of the considerably smaller total UVA doses used in the bath therapy series (Table I). On the other hand, the more frequent flares of PMLE-like pruritic rash in the orally treated patients may partly be related to the higher individual exposures (up to 4–7 J/cm^2 in the majority) as compared with the maximal dose of 0.6 J/cm^2 used in the bath series.

The present study also gives some insight into the mechanisms underlying the hyposensitizing effect of PUVA irradiation. Firstly, the effects were shown to be primarily localized to skin areas receiving both psoralen and UVA (Figs. 1, 2). The enhanced pigmentation of the PUVA-exposed skin areas and the thickening action of photochemotherapy on the corneal layer (2) could possibly suffice to explain this phenomenon. However, other mechanisms, such as Langerhans cell depletion (4), antigen (chromophore) depletion, or a local anti-inflammatory action could influence the polymorphic light reaction, which is considered to be dependent on cell-mediated immune mechanisms (12). While it is difficult to compare, in a meaningful way, the results for erythema production (Fig. 2) and the polymorphic phototest reactions (Fig. 1), the impression remains that the effect may have been more powerful on the PPR. Obviously a more exact knowledge of the mechanisms underlying the abating effect of PUVA exposures on the PLR test could aid in resolving the pathogenetic mechanisms of polymorphous light eruptions.

REFERENCES

1. Ashurst, A.: Light sensitization cured by progressive light desensitization. Practitioner *141:* 220, 1938.
2. Becker, S. W.: Histologic changes in human skin following psoralen therapy. J Invest Dermatol *32:* 263, 1959.
3. Fischer, T. & Alsins, J.: Treatment of psoriasis with trioxsalen baths and dysprosium lamps. Acta Dermatovener (Stockholm) *56:* 383, 1976.
4. Friedmann, P. S.: Disappearance of epidermal Langerhans cells during PUVA therapy. Br J Dermatol *105:* 219, 1981.
5. Hölzle, E., Hofman, C. & Plewig, G.: PUVA-treatment for solar urticaria and persistent light reaction. Arch Dermatol Res *269:* 87, 1980.
6. Gschnait, F., Hönigsmann, H., Brenner, W., Fritsch, P. & Wolff, K.: Induction of UV light tolerance by PUVA in patients with polymorphous light eruption. Br J Dermatol *99:* 293, 1978.
7. Hannuksela, M. & Karvonen, J.: Trioxsalen bath plus UVA effective and safe in the treatment of psoriasis. Br J Dermatol *99:* 703, 1978.
8. Jansén, C. T.: The natural history of polymorphous light eruptions. Arch Dermatol *115:* 165, 1979.
9. — Erythemal and pigmentary phototest reactions in polymorphic light eruptions. Acta Dermatovener (Stockholm) *59:* 499, 1979.
10. — The morphologic features of polymorphous light eruptions. Cutis *26:* 164, 1980.
11. — The polymorphic phototest reaction. Arch Dermatol (in press).
12. Jansén, C. T. & Helander, I.: Cell-mediated immunity in chronic polymorphous light eruptions. Leukocyte migration inhibition assay with irradiated skin as antigen. Acta Dermatovener (Stockholm) *56:* 121, 1976.
13. Johnson, K. J.: Light sensitivity treated by hyposensitization. Ann Allergy *19:* 891, 1961.
14. Morison, W. L., White, H. A. D., Gonzalez, E., Parrish, J. A. & Fitzpatrick, T. B.: Oral methoxsalen photochemotherapy of uncommon photodermatoses. Acta Dermatovener (Stockholm) *59:* 366, 1979.
15. Parrish, J. A., Le Vine, M. J., Morison, W. L., Gonzalez, E. & Fitzpatrick, T. B.: Comparison of PUVA and beta-carotene in the treatment of polymorphous light eruption. Br J Dermatol *100:* 187, 1979.
16. Ramsay, C. A.: Solar urticaria treatment by inducing tolerance to artificial radiation and natural light. Arch Dermatol *113:* 1222, 1979.
17. Väätäinen, N., Hannuksela, M. & Karvonen, J.: Trioxsalen baths plus UVA in the treatment of lichen planus and urticaria pigmentosa. Clin Exp Dermatol *6:* 133, 1981.

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