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Comparison of Topical PUVA with UVA for Chronic Vesicular Hand Eczema

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Topical PUVA was compared with UVA for the treatment of chronic vesicular hand eczema in a double-blind randomized within-patient trial. Twelve of 15 patients completed 8 weeks' treatment and were followed up for 8 weeks. Both sides improved over the 8-week treatment period ($p < 0.05$) and both remained substantially better objectively and subjectively at 8 weeks' follow-up. There was no statistical difference between assessments of the treated hands at any stage. Nine of the patients who completed the study answered a questionnaire up to 18 months later. In 4, eczema was healed, 3 were better on the PUVA-treated hand and 1 on the UVA-treated hand. It is possible that UVA alone is beneficial for chronic hand eczema. ***Key words: Photochemotherapy; Long-wave phototherapy; Hand dermatitis.***

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Oral PUVA has been used successfully for chronic vesicular eczema in both uncontrolled (1,2) and controlled (3,4) studies. Topical PUVA has been shown to be as effective as superficial X-ray therapy for chronic hand eczema (5), which in turn has been shown to be superior to placebo (6). To our knowledge there have been no controlled studies of long-wave ultraviolet radiation (UVA) alone on hand eczema. We compared topical PUVA with UVA on the assumption that UVA would be unlikely to have important therapeutic effects and would therefore be a negative control. Topical rather than oral PUVA was chosen to facilitate a double-blind within-patient study design and to avoid potential systemic side effects for this localized skin disorder.

PATIENTS AND METHODS

Inclusion criteria

All patients were aged 16 years or over. All had had recurrent disabling bilateral symmetrical vesicular hand eczema for at least 6 months with periods of remission (defined as complete clearance) not exceeding 1 month in the previous six. Episodic pompholyx was usually followed by localized swelling, erythema, hyperkeratosis and, sometimes, fissuring. Patients with pustular psoriasis, chronic hyperkeratotic dermatitis and chronic fungal infection were excluded on clinical grounds and by mycological examination, when appropriate. Other exclusion criteria were pregnancy and the need for phototoxic or immunosupperessive drugs. Patients with positive patch tests of current relevance or predominatly irritant dermatitis were not enrolled. The study protocol was approved by the West Birmingham District Medical Ethics Committee.

Patients

Twelve of 15 patients completed the study and were included in the analysis: 9 men, 3 women; mean age (years ± SEM) 49.7 ± 4.1, range 24–69. Five were skin type I, 4 type II, 1 type III and 2 type V. The duration of hand eczema ranged between 2 and 40 years (mean 13.2 ± 4.1). Dorsal and palmar skin (including the fingers) were affected in 11 patients and palmar skin only in 1. The mean area involved by eczema on the backs of the UVA-treated hands (cm^2 ± SEM) was 20 ± 6.9 and on the palms was 73.3 ± 18.6 before treatment. Likewise for the PUVA-treated hands the areas were 19.7 ± 7.0 and 78 ± 18.7. Eight patients also had involvement of the feet and 5 had mild eczema elsewere, most commonly on the arms or legs, though this was not their main problem. Two gave a personal history of asthma, hayfever or childhood eczema and 7 knew a first-degree relative with one of these atopic disorders. All had used moderate to high potency topical steroids prior to the study with little or no apparent benefit, although 9 were still applying them up to the time of inclusion in the study. One had been on systemic steroids for 2 years but had discontinued them 2 months before the study. Eleven were using moisturizers regularly, 2 had used tar preparations and 1 had superficial X-ray treatment 15 years earlier, but none had been treated previously with ultraviolet radiation.

Patch tests

Patients were patch tested to the International Contact Dermatitis Research Group standard series and any other allergens of potential relevance at least 2 months before enrolment. Eight showed one or more positive reactions

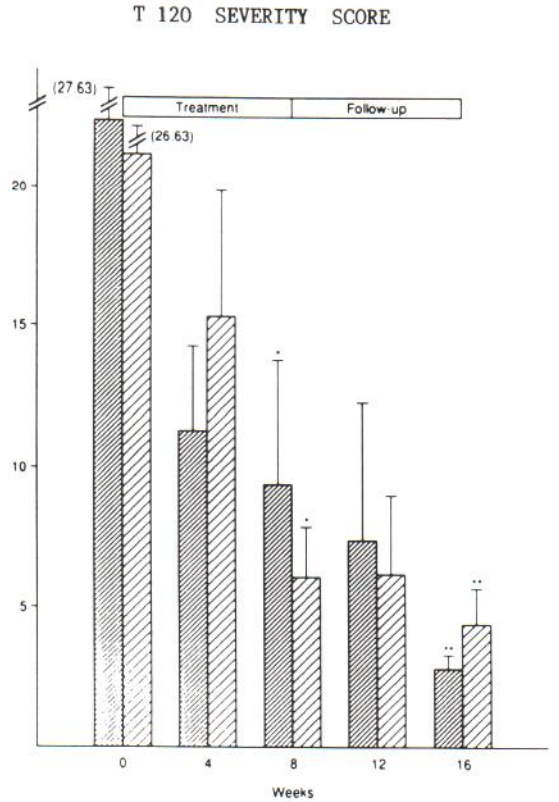

Fig. 1. T_{120} severity scores (see text for details of calculation), means ± S.E.M. * $P < 0.05$ (0–8 weeks), ** P = NS (8–16 weeks), Wilcoxon signed ranks test. Maximum possible score = 120. (▩) PUVA; (▨) UVA.

(nickel sulphate, 3; potassium dichromate, 3; paraphenylenediamine-mix, 1; colophony, 1; cutting fluids, 1; thiuram-mix, 1; balsam of Peru, 1) but none of these allergies was thought to be the primary cause of the chronicity of the eczema as there was no history of continuing exposure.

Withdrawals

Two patients withdrew from the study because they could not attend for regular treatments. One patient had to be withdrawn with a suspected phototoxic eczema affecting the backs of both hands and wrists within a week of starting therapy (total UVA exposure 1 1/2 J/cm^2).

Treatment

Moisturizers alone were applied for a washout period of 1 week before commencing the study and continued throughout the treatment and follow-up phases. Patients were allowed a free choice of moisturizer which included a mixture of liquid paraffin in soft paraffin equal parts, aqueous cream, oily cream, E45 cream (Boots, Nottingham, England) and Lipobase cream (Brocades, Weybridge, Surrey, England). Three patients whose hands flared up badly during the washout period were permitted to use a topical steroid (Dermovate, Glaxo, Greenford, Mdx, England) as

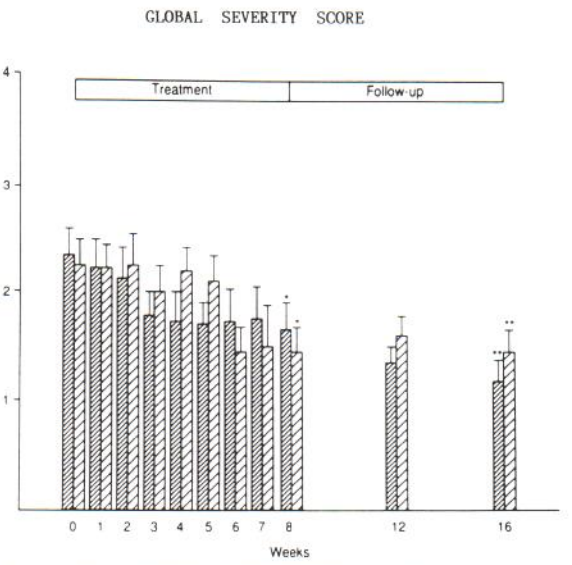

Fig. 2. Global severity scores, means ± S.E.M., * $P < 0.05$ (0–8 weeks), ** P = NS (8–16 weeks), Wilcoxon signed ranks test. Maximum possible score = 4. (▩) PUVA; (▨) UVA.

little as possible during the study, keeping separate tubes for use on each side.

Steroid usage was monitored weekly by weighing the tubes. Psoralen and placebo paints were randomized and coded by one independent investigator (GJS) and supplied

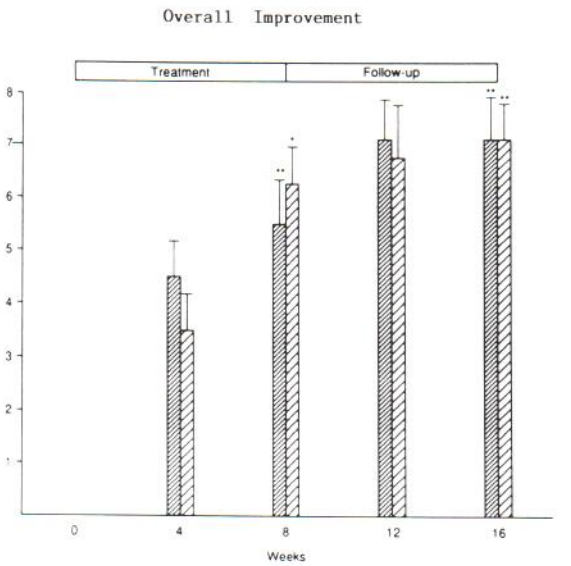

Fig. 3. Visual analogue scales repesenting overall improvement, means ± S.E.M. (higher scores indicate greater improvement). * $P < 0.05$ (4–8 weeks, UVA only), ** P = NS (8–16 weeks), Wilcoxon signed ranks test. Maximum possible score = 10. (▩) PUVA; (▨) UVA.

in bottles labelled left and right. The code was not broken until completion of the study. The active paint was 0.1% 8 methoxypsoralen (Methoxsalen®, Promedica). The placebo paint was the inactive base containing 10% acetone, 10% propylene glycol and 80% ethanol. Patients were shown how to apply the active and placebo paints with a cotton wool bud 1 hour before irradiation and instructed not to apply any other skin treatments on the morning they attended. Paints were washed off the skin immediately after irradiation. Treatments were given three times a week for 8 weeks, starting at 0.5 J/cm^2 and increasing by 0.5 J/cm^2 per treatment to a maximum of 12 J/cm^2. This gentle dose increment was chosen to minimize burning episodes with the topical psoralen. If burning occurred, treatment was discontinued until the reaction had settled and then recommenced at the highest previous dose which had not caused burning.

Light source

Waldmann PUVA 180 and 200 units,containing 8 Philips TL44D25/09N and 14 Sylvania F8T5/PUVA fluorescent tubes respectively, were used in combination. Total UVB output was measured with an IL 1700 radiometer (International Light, Newbury Port, Ma., U.S.A.) and total UVA with a Uvichek radiometer (Rank Hilger). The UVB content of the palmar directed 180 unit was 0.008% of UVA and for the dorsal directed 200 unit was 0.22% of UVA. UVA irradiance was similar for both units, ranging between 5.0 and 9.2 mW/cm^2 over the study period.

Assessment

1) Global rating scales: each hand was assessed at baseline and at weekly intervals during treatment on a 5-point global rating scale (clear 0; minimal 1; mild 2; moderate 3; severe 4);
2) visual analogue scales: patients also completed 10 cm visual analogue scales every 4 weeks to indicate improvement;
3) T_{120} scores: in order to take account of the area of involvement, at well as qualitative parameters of severity, a semi-quantitative scoring system was devised which we called the T_{120} score because the maximum total score was 120. Assessments were made at 0,4 and 8 weeks of treatment and after 4 and 8 weeks of follow-up. The surface area of involvement was measured by tracing the palmar and dorsal outlines of each hand and mapping the active eczema, as defined previously. Absolute areas were calculated by the method of counting squares. Percentage surface areas of eczema were calculated and scored from 0 to 10 (0%, 0; 1–10%, 1; 11–20%, 2; etc. to 91–100%, 10). The number of vesicles on each hand were grouped from 0–4, i.e. (nil, 0;1–25, 1; 26–50, 3; 51–100, 3; 100+, 4). Erythema and scaling were also scored on 5-point scales (absent 0; minimal 1; mild 2; moderate 3; marked 4). The T_{120} was calculated by multiplying the surface area score by the sum of scores for vesiculation, erythema and scaling.

Questionnaire

After completion of the study the patients were sent a questionnaire. They were asked whether their hand eczema had cleared or remained active and, if so, which hand was better. They were also asked what treatments they were currently using.

Statistical analysis

The Wilcoxon matched pairs signed rank test was used for comparison of severity scores, area of involvement and visual analogue scales.

RESULTS

Severity scores

Both PUVA and UVA-treated hands improved over the 8-week treatment period on the T_{120} scoring system (Fig. 1), the global evaluations (Fig. 2) and the visual analogue scales (Fig. 3). The reduction in severity score was significant ($P < 0.005$) for both PUVA- and UVA-treated hands after 8 weeks' treatment on the T_{120} scoring system and global rating scales but only for the UVA-treated hand on the visual analogue scales. Six patients felt that their hands were substantially better at the end of 8 weeks' treatment, 3 experienced some improvement and 3 thought their hand eczema was unchanged. One was able to return to work as a machinist.

A further reduction in severity scores during the 8-week follow-up period did not reach statistical significance on any assessment. Although the PUVA-treated hands improved more rapidly than the UVA side and were less severely affected after 8 weeks' follow-up, these differences were not significant. If the 3 patients treated with topical steroids during the treatment phase of the study are excluded from the analysis, there is no change in the overall pattern of response. Two of the 3 steroid-treated patients improved more on the PUVA-treated hand and showed fewer vesicles on this side.

Area of involvement

On the backs of the hands, the mean area of eczema (cm^2 ± SEM) was reduced from 20 ± 6.9 to 2.9 ± 1.0 ($P < 0.01$) on the UVA-treated side and from 19.7 ± 7.0 to 10.5 ± 5.6 ($P < 0.05$) on the PUVA-treated side. Corresponding reductions in eczema area on the palmar hands were 73.3 ± 18.6 to 32.8 ± 9.6 (P = NS) and 78.0 ± 18.7 to 24 ± 5.1 ($P < 0.02$).

The reduction in surface area is significant for both backs and palms when the data for PUVA and UVA-treated hands are pooled ($P < 0.05$) suggesting

that the greater UVB exposure on the dorsal hands does not account entirely for the improvement.

Associations

There were no significant associations between clinical progress and atopic status, skin type, contact allergies, duration of dermatitis, site of hand involvement or eczema elsewhere after 8 weeks' treatment or at the final follow-up.

Topical steroid usage

Only 3 of the 12 patients who completed the study required topical steroids. There was little difference between the amounts used on the two hands and 1 patient was able to discontinue steroid applications after 4 weeks' treatment.

UVA dose

The mean dose of UVA for the 8-week treatment period was 105.5 J/cm^2 ± 7.8 (SEM), range 70–162.

Side effects

Only 1 patient who completed the study experienced a burning episode on the back of his PUVA-treated hand. The patient who had to be withdrawn developed subacute eczema on the backs of both hands up to her wrists on two occasions. One other patient who withdrew voluntarily developed an acute exacerbation of his eczema, mainly on the PUVA-treated side, on one occasion.

Questionnaire

Nine of 12 patients returned the questionnaire (7 men, 2 women; mean interval between final follow-up and reply 11.6 months ± 2.1, range 1.5–18), of whom 4 were free from hand eczema. One patient had died and 2 could not be contacted. Of the 5 whose eczema remained active, 3 were better on the PUVA-treated hand, 1 on the UVA-treated side and 1 patient thought his eczema was unchanged on both hands. One patient was clear and had discontinued all treatment. Eight others were using moisturizers regularly, 4 of whom were also applying steroid creams.

DISCUSSION

Both UVA- and PUVA-treated hands showed a similar beneficial response. Possible explanations include a placebo effect due to close supervision of the patients and good hand care, a sympathetic response on the UVA-treated side to contralateral PUVA, a therapeutic effect from the small component of UVB in the light source, or a direct response to UVA itself.

The possibility that some of the improvement on the UVA-treated hand resulted from a sympathetic response to the contralateral topical PUVA cannot be completely excluded, as Rosén et al. (3) showed a 92% mean reduction in severity score for the hand treated with oral PUVA and a 49% reduction in the untreated hand, and Jekler & Larkö in their paired comparison study of UVB phototherapy for atopic dermatitis (7) also noted a response on the placebo (visible light) side.

The therapeutic effect of the small UVB content of the lamps is difficult to assess. Rivers et al. attributed a small degree of tanning and changes in Langerhans' cell numbers and peripheral blood lymphocyte subsets, to the minimal UVB output of the fluorescent tubes used in their study (8). UVB irradiances of their lamp units were of the same order of magnitude as the 180 unit in our study but 100 times less than the 200 unit which irradiated the dorsal hands. However, the similar improvement in the dorsal and palmar eczema shown in our study suggests that the therapeutic contribution of UVB was very small. It may bave been more important in the patient who had to be withdrawn with a worsening of eczema on the backs of her hands.

There have been relatively few published studies on the effects of UVA irradiation on eczema in contrast to a large literature on the effects of PUVA (9,10) and UVB (7). Combined UVB and UVA was found to be more effective in inducing remission than UVB in two studies (11,12), although neither was randomized nor double-blind. In an uncontrolled study, Pullmann et al. found that UVA therapy was beneficial for endogenous eczema (13) but no details were given of the irradiation spectrum.

There is increasing evidence that long-wave radiation has biological effects on skin. In Caucasian skin about 50% of incident UVA radiation is absorbed in the epidermis and approximately 30–50% is absorbed in the dermis (14). Therefore many cellular components, including keratinocytes, Langerhans' cells, mast cells and blood vessels could be affected by UVA and perhaps account for a therapeutic effect in eczema. UVA alone has been shown to increase mean epidermal thickness, mean stratum corneum thickness and influence epidermal metabolism (15). Langerhans' cell numbers (16) and

functional membrane markers (17,18) are considerably reduced after UVA exposure in vivo. In healthy volunteers (19), the itch and flare responses to a degranulating stimulus (intradermal 48/80) abated after UVA irradiation, perhaps due to inhibition of a mast cell release mechanism. These studies lend credence to the possibility that UVA may have therapeutic potential and we believe that a comparison of UVA against visible light is now called for.

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