

and 16.5% experienced complete regression of their cutaneous sclerosis.

DISCUSSION

In contrast to what has been achieved with other kinds of treatment, the treatment with drugs inhibiting connective-tissue formation has been shown to bring about partial or complete regression of the dermal sclerosis and a restitution of normal conditions seems to take place. Recent research has provided evidence that sclerodermal collagen is pathological, insofar as the characteristic amino acid of collagen, hydroxyproline, is underhydroxylated in comparison with the normal. Recent studies, yet unpublished (10), failed to demonstrate any restitution of the degree of hydroxylation of proline to hydroxyproline, which would mean that even after treatment the skin collagen remains abnormal.

Although there is some evidence of improvement of the sclerosis of internal organs, e.g. oesophagus, lungs, along with that of dermal sclerosis (2), this problem needs further investigation. The sclerosis of fingers was relatively recalcitrant, probably because of cartilage destruction and fusion of dermis with tendon, joint capsule and periosteal connective tissue. These changes appear to explain why the condition of some patients with severe acrosclerosis does not proceed from grade 3 to grade 4.

The difference between the 1978 and the 1975 results confirms the usefulness of extending the treatment over a long period of time and/or of selecting and combining the most potent drugs.

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Severe Skin Pain after Puva Treatment

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Abstract. Severe skin pain lasting one or two months occurred in 8 of 210 patients treated with PUVA. The pain started 4-8 weeks after the initial dose, mostly about one week after discontinuation of the treatment. It was a prickling, burning pain, usually coming in bouts and confined to limited areas "deep under the skin". In some respects the pain was related to itching, but the patients could easily distinguish between the two sensations. A variety of drugs was tried, but none had any noteworthy effect on this peculiar pain.

Key words: Pain; PUVA treatment

Oral psoralen photochemotherapy (PUVA) can control psoriasis effectively (3, 6, 7) and sometimes ameliorate atopic dermatitis (4), vitiligo (5), and mycosis fungoides (1). During the last 3 years PUVA has been used according to the principles of the European Cooperative Clinical Trial as described by Wolff et al. (7) in the treatment of 210 patients, mostly psoriatics, seen at our department.

The same side effects were observed as those described in other studies on PUVA treatment, viz. erythema, nausea and pruritus (3, 7), as well as less common untoward reactions, such as herpes labialis, hypertrichosis and bleeding beneath the finger nails (2, 4). A further troublesome side effect

Table I. Clinical data about eight patients with pain after PUVA treatment

Patient	Age	Sex	Skin type ^a	MPD (J/cm ²) ^b	No. of treatments	Dose UVA (J/cm ²)	
						Total	Range
1 N. P.	51	M	II	1	26	51.5	0.5-3.5
2 T. J.	54	M	III	3	21	42	2-2.5
3 K. L.	51	M	II	0.5	32	62.5	0.5-3.5
4 S. A.	34	M	III	1.5	24	42.5	1-2.5
5 M. M.	47	F	III	5	15	53	3-4
6 J. F.	25	M	IV	9	17	60	3-4
7 A. P.	35	F	III	3	22	65	2-3.5
8 E. B.	53	F	III	9	15	55.5	3-4.5

^a The following criteria were used: Skintype I = always burn, never tan, II = always burn, then slight tan, III = sometimes burn, always tan, IV = never burn, always tan.

^b MPD = the patient's minimum phototoxicity dose.

of PUVA treatment was severe skin pain, which was noted in 8 of our patients.

CASE REPORTS

Case 1. A 51-year-old man with long-standing psoriasis was treated with PUVA four times a week (Table I). After treatment for 2 weeks, mild transient erythema appeared on the back; after 4 weeks, herpes labialis; and after 6 weeks, intense pain "under the skin" of the trunk. He also reported some itching in the same area. His psoriasis had cleared almost completely and the pain was not confined to previously affected areas. No erythema or other skin lesions were present on the trunk.

The PUVA treatment was discontinued, but the pain persisted. It was most severe at night, even disturbing his sleep. Various analgetics and antihistamines as well as local anaesthetics had no effect on the pain, which persisted for about 2 months, the patient being unable to work for 6 weeks. Itching continued for 1-2 weeks after the pain had stopped (Fig. 1). Laboratory tests revealed nothing remarkable except a transient increase in serum transaminases: S-ASAT 1.9 (normally <0.67 μ kat/l), S-ALAT 2.37 (normally <0.67 μ kat/l). Examination of a biopsy specimen of the liver revealed reactive non-specific hepatocellular changes. No hepatitis Au antigen was demonstrable. Neurologic examination showed nothing abnormal.

Case 2. A 54-year-old man with psoriasis for 30 years was treated with PUVA four times a week for 5 weeks (Table I), after which his psoriasis had cleared and the treatment was discontinued. After treatment for 4 weeks he developed herpes labialis, and after 5 weeks, depigmentation and erythema at the site of a previous discoid psoriatic change over the sacrum.

A few days after the withdrawal of PUVA, severe pruritus occurred in the depigmented area. Two days later the itching changed to severe pain "deep in the skin" in the same area. The pain came in bouts and was most severe at night. An attack could also be provoked by scratching. Each such attack lasted for about 15 min. Various analgetics and antihistamines as well as topical

steroids and local anaesthetics had no noteworthy effect. The bouts of pain persisted for about one month and the patient was unable to work for 2 weeks. Some itching continued for another 2 weeks after the pain had stopped (Fig. 1). Laboratory tests revealed nothing remarkable. The findings at neurologic examination and examination with motor and sensory neurography were normal.

Case 3. A 51-year-old man with psoriasis for 15 years was treated with PUVA four times a week for 8 weeks (Table I), by which time his psoriasis had cleared and treatment was discontinued. During this time the patient had no erythema or any other side effects. One week after discontinuation of treatment the patient got intense pruritus on the back. The itching soon spread to the chest and to the left arm. After about one month the pruritus changed to severe pain in the same areas. No skin lesions were observed. The pain was most pronounced at night and could easily be provoked by scratching. However, it often started spontaneously. Various analgetics and antihistamines as well as transcutaneous nerve stimulation had scarcely any effect. After a further month the pain disappeared from the back, where it had started, and was then confined to the chest and left arm, where it persisted for more than 2 months (Fig. 1). Laboratory tests revealed nothing remarkable.

Case 4. A 34-year-old man with psoriasis for more than 10 years was treated with PUVA four times a week for 6 weeks (Table I), after which about 95% of the affected area had cleared and treatment was discontinued. After treatment for 2 weeks a mild transient erythema had appeared all over the body. One week after discontinuation of treatment the patient complained of a prickling, burning pain "deep under the skin" on the left lower leg and the flanks. He also reported some itching in the same areas. These symptoms were not accompanied by erythema or any other skin lesions. The pain could be provoked by scratching and was most severe at night, when it disturbed his sleep. Various analgetics and antihistamines had no effect. However, transcutaneous nerve stimulation afforded some alleviation from the pain. After one month the pain gradually disappeared over a period of 2 weeks (Fig. 1). Laboratory tests revealed nothing abnormal except an increase in the serum transaminase S-ALAT: 1.3

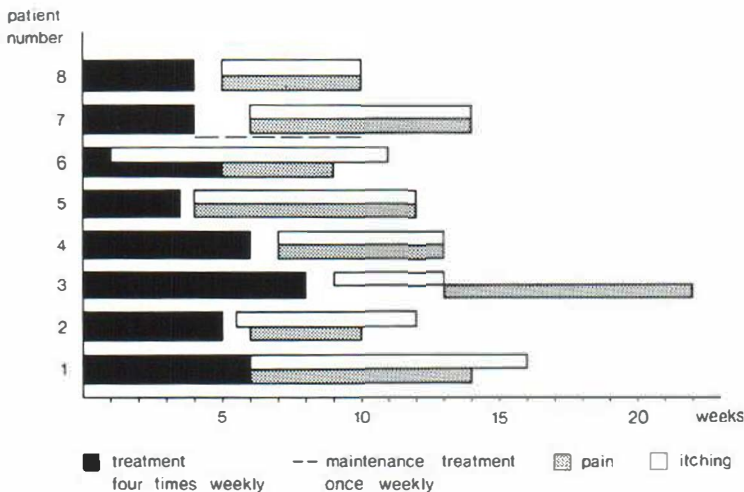


Fig. 1. Duration of PUVA treatment, pain and itching in eight patients.

(normally $<0.67 \mu\text{kat/l}$) which had been observed even before the PUVA treatment.

Case 5. A 47-year-old woman with bronchial asthma and psoriasis since early childhood was treated with PUVA four times a week for 3½ weeks (Table I), after which her psoriasis had practically cleared and the treatment was discontinued. After treatment for 2 weeks she had developed mild erythema on the buttocks and after 3 weeks also on the feet. A couple of days after discontinuation of treatment she complained of itching on the back and abdomen. When the affected area was scratched, the pruritus changed to severe pain "under the skin". At that time she had no erythema or other skin lesions. The symptoms were most severe at night. The itching could be provoked by heat. Pain provoked by scratching generally persisted for about 15 min. Antihistamines and analgetics had no effect. The symptoms persisted for nearly 2 months (Fig. 1). Laboratory tests revealed nothing remarkable.

Case 6. A 25-year-old man with psoriasis for more than 10 years was treated with PUVA four times a week for 5 weeks (Table I). After four treatments he complained of itching on the buttocks. This area was therefore screened off with a piece of cloth during the subsequent treatments. No erythema or any other skin lesions were seen. However, after 5 weeks, the pruritus developed into pain and PUVA was withdrawn. His psoriasis had by then practically cleared. The pain usually started with itching of the skin, which when scratched developed into intense, peculiar, prickling pain "deep in the skin". Usually the attacks lasted for about 20 min, but sometimes for 3 or 4 hours. The symptoms were most pronounced at night and disturbed his sleep. Antihistamines and analgetics had no effect. After about one month the pain subsided, but the pruritus persisted for another 2 weeks (Fig. 1). Laboratory tests revealed nothing remarkable.

Case 7. A 35-year-old woman with severe atopic dermatitis since early childhood was treated with PUVA four times a week for 4 weeks, then once a week for 6 weeks (Table I). The dermatitis had almost cleared, but gradually exacerbated during the maintenance treatment. After two

maintenance treatments she felt a peculiar prickling pain "deep under the skin" on the forearms. After a further 3 weeks the pain spread to the lower legs and the treatment was discontinued. There was mild dermatitis with excoriations not only on the arms and legs, but also on other parts of the body. The prickling pain was most severe at night and could sometimes be provoked by scratching. The pain came in bouts lasting for several hours and sometimes persisted the whole night. Analgetics and antihistamines, topical steroids and local anaesthetics had scarcely any effect. After discontinuation of the PUVA maintenance treatment the pain continued for 3 weeks on the arms and for 4 weeks on the legs (Fig. 1). Laboratory studies revealed nothing remarkable.

Case 8. A 53-year-old woman with psoriasis for more than 30 years was treated with PUVA four times a week for 4 weeks (Table I). The psoriasis had cleared by then and the treatment was discontinued. During treatment the patient experienced no erythema or any other side effects, but one week after discontinuation of treatment she complained of intense itching on the left buttock. The itching could be provoked by exposure to heat and by pressure. Sitting was therefore extremely uncomfortable. When she scratched the skin the pruritus changed to severe pain "deep in the skin". The reaction lasted for about 2 hours. When she scratched the left buttock, she experienced pain also in the dorsal surface of the left lower leg, where she had never noticed any itching. There was neither erythema nor any other skin lesions. The symptoms were most pronounced at night. Antihistamines and analgetics had scarcely any effect. After 4 weeks the pain disappeared from the left leg but persisted on the left buttock for another 1–2 weeks (Fig. 1).

Laboratory studies revealed nothing remarkable. Histopathological examination did not show any abnormal nerve structures. In the upper parts of the corium the capillaries were slightly dilated. Examination by direct immunofluorescence demonstrated fibrinogen in vessels in the whole corium. No demonstrable IgM or C'3. The results suggested inflammation at the vessels without complement activation or immunological findings. Neu-

rophysiological examination showed that the appreciation of temperature was intact and equal on both sides. This findings argued against a generalized irritative affection of thin afferent nerve terminals in the skin and indicated a selective stimulation of nociceptive afferents.

DISCUSSION

Of 210 patients treated with PUVA, 8 reported severe pain "deep in the skin". The pain was described in a similar way by all 8 patients. It was of a peculiar type and none of the 8 patients had ever felt anything like it before. At our department such pain has been reported only in these PUVA-treated patients. It was a prickling, burning pain "deep under the skin" and quite different from itching. The pain usually came in bouts lasting 15 minutes up to several hours. The attacks could start spontaneously or be provoked by scratching of or pressure on the skin. They were invariably most intense at night and usually disturbed the patients' sleep. The skin pain occurred in limited areas which did not coincide with the dermatomes.

Itching is a rather common side effect of PUVA treatment. In all these patients the pain had some correlation to itching, which could occur before, after and together with the pain in the same areas (Fig. 1). However, the patients clearly distinguished between these two sensations.

Seven of the patients had psoriasis vulgaris and one had atopic dermatitis. The pain occurred in normal-looking skin unrelated to previous skin lesions except in one patient who had depigmentation and one who had mild dermatitis in the area of the pain.

The pain was related to details in the PUVA treatment in the following respects:

1. It is usually started 1-2 months after the beginning of PUVA treatment (Fig. 1). In 5 of the patients it started about a week after discontinuation of the treatment. In the others the treatment was discontinued because of the pain (Fig. 1).
2. Four patients had mild local erythema during the treatment, but only in case 2 was the pain confined to the area of the preceding erythema. Two of the patients had herpes labialis during the therapy.
3. The total and maximum UVA doses were invariably rather small (Table I). There was no obvious correlation between the occurrence of pain and the skin type and MPD of the patients (Table I).
4. During the treatment the patients used as topical therapy carbamidum 10%, aqua purificata 20%

in a neutral ointment base (ung. Merck®). Furthermore, they used a bath oil containing liquid petrolatum and as emulsifier a synthetic phospholipid (Hostaphat®, Hoechst).

The pain demanded treatment due to its intensity, but various analgetics and antihistamines, topical steroids and local anaesthetics had scarcely any effect. It lasted for 1-2 months and 2 of the patients were unable to work for some weeks. All the 8 patients were emotionally well-balanced persons and reported their symptoms independently of each other. None of the patients could ever think of undergoing this treatment again, even though it had had such a beneficial effect on their skin disease.

In a couple of cases, neurological examination, motor and sensory neurography, histopathological examination and examination by direct immunofluorescence revealed nothing remarkable. In one patient (case 8) neurophysiological examination indicated a selective stimulation of nociceptive afferents in the skin. There were no signs of a generalized peripheral neurotoxic influence. However, the pathophysiological mechanism of this painful side effect of PUVA treatment remains obscure.

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