

PHOTOTOXICITY OF TOPICAL TRIOXSALEN

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Abstract. The phototoxic properties of topical trioxsalen preparations were studied in 73 test subjects. A W/O emulsion base was superior to petrolatum, O/W emulsion, double emulsion and carbowax. The optimal interval between application of the drug and UVA irradiation varied between 40 and 60 min for both cream and ointment bases. An occlusive dressing greatly enhanced the phototoxic effect of the drug. The skin lost photosensitivity in 4 hours when the preparations were removed from the skin 45 min after the application. For clinical use a proper concentration of trioxsalen in emulsion bases was 0.01-0.1%. Both W/O and O/W emulsion bases with 0.01% trioxsalen locally applied gave moderate or good clinical results in 16 psoriatics and in 4 patients with lichen planus. W/O emulsion being better in this respect.

Key words: Photo-epicutaneous testing; Photochemotherapy; PUVA; Trioxsalen

Two active psoralens are presently in routine clinical use, namely trioxsalen (4,5',8-trimethylpsoralen) and methoxsalen. The latter is more effective when given orally (6), but trioxsalen is more active in local use (2). Trioxsalen bath (50 mg/150 l water) with a low UVA dose is effective in the treatment of both psoriasis (3) and nodular prurigo (17). An alternative method using trioxsalen baths and dysprosium lamps, giving both UVB and UVA, is also effective in the treatment of psoriasis (1, 2).

Suhonen (15) has shown in his studies on the phototoxicity of topically applied methoxsalen, that the vehicle plays a very important role in the penetration of this drug in the skin. The phototoxic properties of trioxsalen in various vehicles were studied in this investigation. The results showed that W/O emulsion base was superior to cream bases and petrolatum in both producing phototoxic reactions and in local PUVA treatment of psoriasis and lichen planus.

MATERIAL AND METHODS

Patients

Sixty-two out of 73 test subjects were voluntary dermatological patients; 42 of them had psoriasis, 11 lichen

planus, 4 nodular prurigo and 5 had acne vulgaris. Eleven of the test subjects belonged to the staff of our clinic. The series comprised 45 males, mean age 45 (range 20-71) years and 28 females, mean age 44 (range 15-81).

Materials

The UVA source was an ordinary PUVA-cabin giving 12 mW/cm² of UVA (PUVA 22, Astra-Sjuco, Helsinki). Trioxsalen (Fermion, Finland) was used as the phototoxic substance in six different vehicles: Aqualan®,¹ Novalan®, Ambilan®, Hydran® (all from Orion Corporation Ltd, Helsinki, Finland). Yellow petrolatum and carbowax. The mean amount of the test substance applied to the skin was 20 µl/cm².

Methods

The optimal interval between application of trioxsalen and UVA irradiation was studied with 0.1% trioxsalen in Aqualan® and Hydran®. Each test substance was applied to a 3×20 cm area of back skin having a normal appearance. No occlusion was used but the area

¹ Aqualan®

Emulgators	30 g
Glycerol (85%)	8 g
Methyl parahydroxy-benzoate	250 mg
Purified water ad	100 g

Ambilan®

Emulgators	20 g
White petrolatum	20 g
Paraffin liquidum	10 g
Sorbic acid	200 mg
Purified water ad	100 g

Carbowax (Ungt. Macrogoli DF)

Macrogolum 400	60 g
Macrogolum 300	40 g

Novalan®

Emulgators	32 g
White petrolatum	8 g
Methyl parahydroxy-benzoate	100 mg
Purified water ad	100 g

Hydran®

Emulgators	6 g
White petrolatum	54 g
Sorbic acid	200 mg
Purified water ad	100 g

Table 1. The number of positive reactions and mean reaction indices with 0.1% trioxsalen in six different vehicles

The drug was applied 45 min before irradiation with 1.4 J/cm² of UVA. Aqualan®=O/W emulsion. Novalan®=O/W emulsion. Ambilan®=double emulsion. Hydran®=W/O emulsion. Carbowax=Macrogol 400+3000. 0=no reaction, 1=erythema, 2=erythema with oedema, 3=moderate or strong oedema, 4=blisters or uniform bulla

Vehicle	No. of tests	No. of positive reactions	Mean reaction indices	No. of bullae
Aqualan®	21	6	0.3	0
Novalan®	21	6	0.3	0
Ambilan®	21	20	1.2	0
Hydran®	21	21	3.1	6
Petrolatum	21	20	1.8	0
Carbowax	21	0	0	0
Aqualan® with occlusion	21	21	2.5	0

was protected from light until irradiation. After 5, 10, 20, 30, 40, 50, 60, 90, 120, 150 and 180 min 1 cm × 1 cm areas were irradiated with 2.2 J/cm² of UVA. Just before irradiation each test area was cleansed of test substances by pressing several times with blotting paper. The test areas were protected from light for a further 24 h and the results were recorded 72 h after irradiation.

In the second part of the study the phototoxicity of trioxsalen was investigated in six cream and ointment bases. The concentration of the drug was 0.1%. Each test substance (20 µl/cm²) was applied to a 3 cm × 3 cm area of normal back skin. Trioxsalen-Aqualan® was applied to two areas with and without occlusive plastic wrap. Other test areas were not occluded but were protected from light. After 45 min the test substances were removed by pressing several times with blotting paper, avoiding spread of vehicles. The test areas were covered with a light-proof carbon paper with 1 cm × 1 cm hole for each vehicle and irradiated with 1.4 J/cm² of UVA. The skin under the carbon paper between the test squares functioned as a dark control. The test areas were protected from further light for 24 hours. The readings were made 72 hours after irradiation.

In the third part of the study the disappearance of the phototoxicity after removing trioxsalen from the skin was investigated. Hydran® with 0.01% trioxsalen was removed 45 min after application from the right forearm with blotting paper and from left forearm with soap and warm water. The test areas were protected from further light exposure until UVA irradiation. The exposure to UVA was performed with increasing doses (Table II) 0, 2, 4, and 8 h after the removal of the drug. The test results were read 72 h after irradiation.

The ability of 0.01% trioxsalen in cream and ointment bases to clear up dermatoses was studied in 16 patients with psoriasis and 4 patients with lichen planus. Trioxsa-

len-Aqualan® was applied to the right arm and trioxsalen-Hydran® to the left arm, other areas of the body and legs were treated with trioxsalen baths as described by Hannuksela and Karvonen (3). 35 min after application of the ointments the patients took a trioxsalen bath for 10 min, after which both the ointments were removed with blotting paper and UVA irradiation was given as described earlier (3).

RESULTS

Optimal penetration time

The optimal interval between application of trioxsalen and UVA irradiation was 40–60 min for trioxsalen-Aqualan® (Fig. 1). After this period the phototoxicity diminished rapidly even if the drug was not removed from the skin. After application of trioxsalen-Hydran® the phototoxicity reached its maximum in 50 min and remained strong for at least 3 hours.

Vehicles

The intensity of phototoxic reaction to trioxsalen was strongly influenced by the vehicle (Table I). No positive reaction was seen when Carbowax was the vehicle. Pure petrolatum and Ambilan® gave satisfactory results, but the best results were gained with Hydran®.

When 0.1% trioxsalen-Aqualan® was occluded for 45 min before irradiation the number and the intensity of positive reactions increased greatly, nearly achieving the grade of phototoxicity of 0.1% trioxsalen-Hydran® applied without occlusion.

Disappearance of phototoxicity

After removing trioxsalen-Hydran® from the skin, the phototoxicity disappeared rapidly (Table II). After as little as 2 hours the reactions were greatly weakened and after 8 hours even 21.6 J/cm² failed to produce a reaction. This was observed irrespective of whether the trioxsalen ointment was washed from the skin or removed with blotting paper.

Treatment of psoriasis and lichen planus

In 16 out of 20 patients with psoriasis or lichen planus the lesions healed more rapidly with 0.01% trioxsalen-Hydran® than with 0.01% trioxsalen-Aqualan® (Table III, Figs. 2a, 2b). On the other hand, trioxsalen-Hydran® and trioxsalen bath were equally effective. Tanning after trioxsalen ointment therapy was just as even as after trioxsalen bath therapy. Degree I burning was seen with trioxsalen

Table II. Disappearance of phototoxicity after removal of trioxsalen from the skin of 12 test subjects

Trioxsalen-Hydran® (0.01 %) was removed 45 min after application

Time after removal of the drug (h) ...	Drug removed with blotting paper				Drug removed with soap and water			
	0	2	4	8	0	2	4	8
UVA dose (J/cm ²)	0.96	3.84	7.20	21.6	0.96	3.84	7.20	21.6
Number of positive test reactions	12	10	0	0	12	10	0	0

bath in 2 cases, with trioxsalen-Hydran® in 4 cases and with trioxsalen-Aqualan® in one case. There were no pathological changes in routine blood and urine tests due to trioxsalen.

DISCUSSION

The phototoxicity of topical trioxsalen was highly dependent on the vehicle, as could be expected on the basis of the studies concerning methoxsalen (4, 5, 15). The finding that lipophilic ointment, Hydran®, was the optimal vehicle for trioxsalen was somewhat unexpected, because the best vehicles for methoxsalen were petrolatum, foundation cream and hand cream in study of Suhonen (15), and hydrophilic ointment and lanolin in that of

Kaidbey & Kligman (4). When trioxsalen-Aqualan® was used with occlusion the phototoxic reactions were greatly enhanced, and thus one of the most important factors in sensitizing the skin to phototoxic substances seems to be the degree of occlusion. Perhaps also the poorer solubility of trioxsalen in water (2 mg/100 ml) compared with methoxsalen (4.8 mg/100 ml) (9) has an effect on the penetration of the drug.

The optimal interval between the application and irradiation was 40–60 min for cream base (Aqualan®) and slightly longer for trioxsalen in lipophilic base (Hydran®) when they were applied without occlusion. Suhonen (15) found that 1–2 h was the optimum for methoxsalen in various vehicles applied with occlusion.

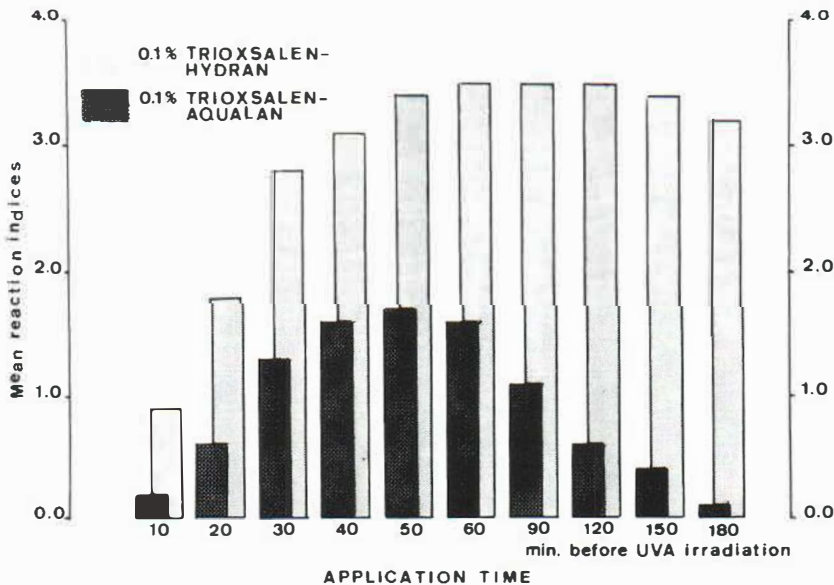


Fig. 1. Mean 72 h reaction indices of reactions elicited by 0.1 % trioxsalen-Aqualan® and 0.1 % trioxsalen Hydran® irradiated with 2.2 J/cm² of UVA in 20 test subjects. Time means the interval between application and irradiation. Reaction indices: 0=no reaction, 1=erythema, 2=erythema with oedema, 3=moderate or strong oedema, 4=blisters or uniform bulla.

Table III. Results of the treatment of psoriasis and lichen planus with 0.01 % trioxsalen in Aqualan® and in Hydran® and with trioxsalen baths (50 mg/l 150 l water)

The mean number of treatment sessions in the psoriasis group was 16 and the mean total dose of UVA 13.1 J/cm². In lichen planus the corresponding figures were 15 and 6.1 J/cm²

	Psoriasis (16 pats.)			Lichen planus (4 pats.)		
	Moderate ^a	Good	Excellent	Moderate	Good	Excellent
Trioxsalen-Aqualan® (right arm)	4	10	2	3	0	1
Trioxsalen-Hydran® (left arm)	0	8	8	0	3	1
Trioxsalen bath (body and legs)	0	7	9	0	3	1

^a Poor: healing under 30%. Moderate: 30–60%. Good: 60–90%. Excellent: 90–100%.

When trioxsalen-Hydran® was left on the skin for 3 hours there was almost no decrease in the strength of phototoxic reactions, whereas after cleaning with a paper the phototoxicity rapidly disappeared (Table II). This rapid loss of photosensitivity is especially important in summertime when avoidance of sunlight may be difficult.

The results of treatment with trioxsalen ointments correlates well with results with bathing PUVA (Table III). The proper concentration of trioxsalen was only 1/10–1/100 of that needed in topical methoxsalen preparations (8, 10, 11, 12, 13). This finding is in agreement with that reported by Fischer & Alsins (2).

The psoralens readily penetrate the skin and reach the blood stream (5). Trioxsalen is obviously

rapidly transformed into non-photosensitizing moieties (7), thus reducing the possibility of untoward side effects. This concept is supported by the findings of Hannuksela & Karvonen (3) according to which the skin areas which were not immersed in the trioxsalen bath during psoriasis therapy did not become photosensitive.

Psoralens, administered topically or intraperitoneally, with ultraviolet radiation have been shown to be potent carcinogens in laboratory animals (16). In some psoriatics treated orally with methoxsalen, there may be a risk of cutaneous carcinoma (14). Until now no carcinomas have been reported following the use of trioxsalen and UVA in man, but a careful follow-up of the patients who underwent this treatment is warranted.



Fig. 2a. The hands of a 52-year-old male with papular lichen planus before local photochemotherapy.



Fig. 2b. Within 19 days, left side treated with 0.01% trioxsalen-Hydram® nearly healed with rather pronounced tanning, but the right side treated with 0.01% trioxsalen-Aqualan® healed only partly.

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