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Table I. *Staining (S) and erythema (Er) by 24-hour exposure of 0.05% dithranol (D), 10-acetyldithranol (2C), 10-propionyldithranol (3C) and 10-butyryldithranol (4C) in 50 psoriasis patients*

Grading 0–3

S	Er	D	2C	3C	4C
0	0			16	44
0	1	3	19	26	6
0	2	23	27	8	
1	1	1			
1	2	23	4		
Total		50	50	50	50

Irritation and Staining by Dithranol (Anthralin) and Related Compounds: II. Structure-Activity Relationships among 10-Meso-Substituted Acyl Analogues

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Abstract. Irritation and staining by dithranol and some 10-meso-substituted acyl analogues was studied with the chamber-testing technique in a series of 50 psoriasis patients. The test concentrations for dithranol, 10-acetyldithranol, 10-propionyldithranol and 10-butyryldithranol were 0.05 and 0.5%, for 10-valeryldithranol 5% and for 10-myristoyldithranol 10%. As a rule, with increasing length of the carbon chain of the 10-acyl substituent (from 2C to 14C) the staining and irritative properties of the molecule decreased.

Key words: Psoriasis; Dithranol; Anthralin; 10-Acyl-1,8-dihydroxy-9-anthrones; Delayed skin irritation; Staining of the skin; Chamber test

In a previous paper (3), skin irritation [1, 2] and staining caused by dithranol and some related anthrones was studied by applying the chamber-testing technique of Pirilä (4). In order to reduce the staining and the irritation either one or both of the hydrogen atoms of the reactive methylene group at the 10-meso-position of dithranol was replaced. When both hydrogen atoms were replaced to form 10,10'-*bis* (formylethyl) dithranol, the new molecule had lost not only the irritative and staining properties of dithranol but also the antipsoriatic activity of the parent compound (cf. 6). When only one of the two hydrogen atoms was replaced with an acetyl group to form 10-acetyldithranol, the new molecule retained most of the properties of dithranol.

In this paper, it is shown that with increasing length of the carbon chain of the 10-acyl substituent the staining and even the irritative activities of the molecule decrease.

MATERIALS AND METHODS

An unselected series of hospitalized psoriasis patients was tested. The test compounds dithranol (D), 10-acetyldithranol (2C), 10-propionyldithranol (3C), 10-butyryldithranol (4C), 10-valeryldithranol (5C) and 10-myristoyldithranol (14C) were pure samples synthesized[2] by Erkki Honkanen, Ph.D. and Aino Pippuri, MSci (Orion Pharmaceutical Co., Helsinki, Finland). The proper concentrations of the test compounds were screened by testing on the back skin of the author. The concentrations selected were 0.05% and 0.5% for D, 2C, 3C and 4C. For 5C and 14C the concentrations were 5% and 10%, respectively. The chamber-test method was applied as described (3). The diameter of the erythema, edema and brownish stain was measured and the visual intensity estimated using a scale graduated from 0 to 3. When staining hampered the estimation of erythema, contact thermography was used.

[1] Irritation is defined as non-immunologic local inflammatory reaction of the skin, characterized by erythema, edema or corrosion, following topical application of a chemical substance (cf. 2).

[2] Patents pending.

Table II. *Staining (S) and erythema (Er) by 24-hour exposure of 0.5% dithranol (D), 10-acetyldithranol (2C), 10-propionyldithranol (3C) and 10-butyryldithranol (4C) in 50 psoriasis patients*

Grading 0–3

S	Er	D	2C	3C	4C
0	1			17	26
0	2			19	20
0	3			2	
1	2	9	4	7	1
1	3			5	3
2	2	25	19		
2	3	11	15		
3	2	1	1		
3	3	4	11		
Total		50	50	50	50

Table III. *Staining (S) and edema (Ed) by 24-hour exposure of 0.05% dithranol (D), 10-acetyldithranol (2C), 10-propionyldithranol (3C) and 10-buryryldithranol (4C) in 50 psoriasis patients*

Grading 0–3

S	Ed	D	2C	3C	4C
0	0	3	12	39	50
0	1	5	23	9	
0	2	16	7	2	
0	3	2	4		
1	1	5	3		
1	2	18	1		
1	3	1			
Total		50	50	50	50

Table IV. *Staining (S) and edema (Ed) by 24-hour exposure of 0.5% dithranol (D), 10-acetyldithranol (2C), 10-propionyldithranol (3C) and 10-buryryldithranol (4C) in 50 psoriasis patients*

Grading 0–3

S	Ed	D	2C	3C	4C
0	0			9	16
0	1			20	23
0	2			9	7
1	0	1			
1	1	1			1
1	2	7	4	9	
1	3			3	3
2	1	5	4		
2	2	29	26		
2	3	2	4		
3	2	4	5		
3	3	1	7		
Total		50	50	50	50

RESULTS AND DISCUSSION

Irrespective of the compound tested, the peak of the inflammatory reaction expressed either as erythema or as edema was reached within 3 days, usually by the second-day reading (cf. 1), when the brownish stain too had gained its darkest shade without signs of peeling-off. The test results for D, 2C, 3C and 4C in 50 psoriasis patients are compiled in Tables I–IV. As can be seen, the staining and irritative properties of the molecules decrease with increasing length of the carbon chain (2C, 3C, 4C) of the acyl substituent. To date, 32 patients have been tested with 5% 5C: one exhibited no reaction at all, 8 showed grade 1 erythema, 20 grade 2 erythema and 3 grade 3 erythema. Slight to marked edema was seen only in patients with moderate to marked erythema. Only 5 of the 32 patients developed a slight grade 1 staining with grade 2 to 3 erythema. None of the 50 patients tested with 10% 14C developed staining and only 7 showed a faint erythema reaction.

Apparently, the bulkier the 10-acyl substituent, the greater is the steric hindrance to the staining reactions, i.e. to the dimer and polymer formation. Steric hindrance may play a role also in the decrease in the inflammatory reactions occurring with increasing length of the carbon chain of the 10-acyl substituent, because the parent compound dithranol has been proposed to be a prostaglandin agonist fitting well into the prostaglandin receptors of the cell membranes (cf. 3). Differences in molecular size and polarity among these hydroxyanthrones also influence their diffusivity through the horny layer.

In a previous study (3), I considered it worthwhile to continue the search for "a fourth generation" of antipsoriatic hydroxyanthrones causing less irritation and little if any staining, i.e. antipsoriatics with better patient acceptability. Whether such a fourth generation will arise from the 10-acyl derivatives of dithranol remains to be seen. It seems to be ethically justified to start phase I clinical trials with these derivatives because at least two of them, namely 2C and 14C (5), are not stronger tumour promoters in mice than is the parent compound dithranol, which has proved over 60 years of widespread therapeutic use to be free from serious side effects.

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Photochemotherapy for Alopecia Areata

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Abstract. Ten patients with alopecia areata (plaque type and totalis type) were treated with oral photochemotherapy. Successful results were obtained in 7 cases. No side effects were noted. Hair growth was related to the energy delivered and was not dependent on the duration of the disease. No relapses occurred after discontinuation of the treatment. The hypothesis concerning the mechanisms of hair regrowth are discussed.

Key words: Alopecia areata; 8-MOP; Photochemotherapy

Alopecia areata (AA) is a disease of unknown origin. Alopecia totalis and alopecia universalis are the most severe forms, and the prospect of spontaneous hair growth are very poor. Up to the present, therapy has consisted of corticosteroid drug administration, either intralesional, topical, or systemic (9). New treatment modalities have been recently proposed, using sensitization to dinitrochlorobenzene (DNCB) (1, 3, 6), and topical photochemotherapy (8, 10). We present data obtained from 10 patients with AA treated with oral photochemotherapy.

PATIENTS AND METHOD

Ten patients were studied—8 men and 2 women. Their ages ranged from 11 to 48 years. 5 patients had AA with multiple plaques and 5 had alopecia totalis. The duration of the disease ranged from 2 months to 16 years. Informed consent was obtained from all participants.

Light source. Hexagonal stand-up light boxes containing 84 fluorescent tubes mounted side by side in a vertical plane were used as UVA source. These tubes have a continuous spectrum of high intensity irradiation between 320 and 400 nm with a peak emission at 365 nm. The energy delivered was, on average, 8-8.5 mW/cm² at a distance of 50 cm.

8-methoxypsoralen (8-MOP). Ten-milligram capsules of 8-MOP were given 2 hrs prior to UVA exposure, according to the patient's weight (from 10 mg for 25 kg or less, up to 60 mg for weights greater than 90 kg).

Table I.
M. P = multiple plaques, A. T = alopecia totalis

Case no.	Age	Sex	Clinical form	Duration	Energy (J/cm²)	No. of irradiations	Hair growth (%)
1	48	M	M. P	6 mo.	84	14	90
2	22	M	M. P	6 mo.	406	36	90
3	44	M	M. P	2 mo.	444	50	100
4	11	M	M. P	1 yr.	312	46	0
5	27	M	M. P	8 mo.	430	50	90
6	30	F	A. T	16 yrs.	218	24	0
7	12	F	A. T	11 mo.	392	40	0
8	27	M	A. T	3 yrs	784	80	90
9	32	M	A. T	10 yrs	685	69	90
10	18	M	A. T	10 yrs	729	65	100