Acta Derm Venereol (Stockh) 1984, 64: 63–66

Antipsoriatic Activity of 10-Acyl Analogues of Dithranol (Anthralin)

I. *Phase I Clinical Trial of 10-Propionyl Dithranol and 10-Butyryl Dithranol (Butantrone)*

K. K. MUSTAKALLIO and H. BRANDT

Department of Dermatology, Helsinki University Central Hospital, Helsinki, Finland

Mustakallio KK, Brandt H. Antipsoriatic activity of 10-acyl analogues of ditranol (anthralin). I. Phase I clinical trial of 10-propionyl dithranol and 10-butyryl dithranol (butantrone). Acta Derm Venereol (Stockh) 1984; 64: 63–66.

Dithranol, 10-propionyl dithranol and 10-butyryl dithranol were compared as regards their antipsoriatic, staining and irritative properties. They were applied under 12-mm Finn-chambers on the lesional skin of 17 psoriasis patients every second day for 20 days. In 9 patients their concentration was equimolar (2 mmol/kg of white petrolatum) corresponding to 0.05% dithranol, and in 8 patients the concentrations were 2, 4, and 8 mmol for dithranol, 10-propionyl dithranol and 10-butyryl dithranol, respectively. Without regard to the concentration, they all produced under occlusion almost equal thinning of the lesions, but when a 2 mmol concentration was used, 10-butyryl dithranol (butantrone) showed least staining and irritation on the treated sites. *Key words: Psoriasis; Dithranol; Anthralin; 10-Propionyl dithranol; 10-Butyryl dithranol; Butantrone; Antipsoriatic activity; Irritation; Staining.* (Received January 28, 1983.)

K. K. Mustakallio, Department of Dermatology, University Central Hospital, Snellmaninkatu 14, SF-00170 Helsinki 17, Finland.

> "Less irritating and non-staining anthralin preparations should be developed" (1).

To develop for ambulatory treatment of psoriasis less irritating and less staining dithranol (anthralin) preparations, a series of 10-acyl analogues of dithranol has been synthetized and tested "on tiny areas of human skin", as recommended in a statement concerning "Research needs in 11 major areas in dermatology" (1).

10-acetyl dithranol in low concentrations was found to be less irritating and less staining than dithranol but at the 0.5% level it appeared to irritate and stain even more than dithranol (4). However, with increasing length of the carbon chain of the 10-acyl substituent, the irritating and staining properties of the analogues wane (5). In a recent study, dithranol, 10-propionyl dithranol and 10-butyryl dithranol were compared as regards their cumulative irritancy and staining when repeatedly applied to the uninvolved dorsal skin of psoriasis patients. In equimolar concentrations, dithranol caused more irritation and staining than 10-propionyl dithranol, whereas 10-butyryl dithranol irritated and stained less than 10-propionyl dithranol (3).

In the present study, the antipsoriatic activity of these hydroxyanthrones was tested on the lesional skin of the same psoriasis patients using the same technique, i.e. repeated occlusive application on confined small areas of the skin. Preliminary data of this study have been presented as parts of two scientific posters (6, 7).

MATERIALS AND METHODS

17 hospitalized psoriasis patients volunteered for this study. They all had untreated psoriasis plaques of small to medium size and mostly of medium thickness. The thickness of the lesions was estimated

by palpation, using the following scale: 3 = thick plaque; 2 = plaque of medium thickness; 1 = thin plaque, and 0 = no palpable lesion. The reading scale of staining was the same as before (4): 3 = dark brown; 2 = reddish brown; 1 = brownish hue, and 0 = no staining. Increase in lesional redness or oedema was recorded as irritation.

Dithranol, 10-propionyl dithranol and 10-butyryl dithranol were applied under occlusion on identical small plaques. The vehicle, white petrolatum, was applied as a control. For occlusion, 12-mm Finn-chambers were used, being fixed with 5 × 5 cm Scanpor® tapes (8). The contact time per application was 2 days, and the applications were repeated every second day on exactly the same sites.

In 9 patients (Group I) the concentration of the three hydroxyanthrones was 2 mmol/kg of white petrolatum, corresponding to 0.05% dithranol. In 8 patients (Group II) the respective concentrations were 2, 4 and 8 mmol for dithranol, 10-propionyl dithranol and 10-butyryl dithranol. The thickness of treated sites, staining, and potential irritation were recorded before every application, and the trial was continued for 20 days. The lesions not covered by the 5 × 5 cm Scanpor® tapes were subjected to routine treatment with dithranol pastes.

RESULTS

Group I. In the 9 patients treated with 2 mmol concentrations of dithranol, 10-propionyl dithranol and 10-butyryl dithranol the initial mean thickness of the psoriatic plaques was 2.4 units. In all of them the treated sites became within 20 days almost non-palpable (mean reading 0.3) (Fig. 1). At the end of the trial there remained some redness in the lesions in several cases, but the treated sites could attain almost a normal skin colour (Fig. 2). As a rule, the lesions of the untreated areas under the 5 × 5 cm Scanpor® tapes did not improve, but in most patients even the occluded vehicle caused definite but smaller thinning of the treated sites (mean reading 1.2; cf. Fig. 1).

Even though the three hydroxyanthrones showed almost identical antipsoriatic activity, 10-butyryl dithranol was the least staining of them. The mean top-readings of staining were 0.7, 1.1 and 1.9 for 10-butyryl dithranol, 10-propionyl dithranol, and dithranol, respectively. One patient showed initial transient irritation at the sites treated with all three hydroxyanthrones, another displayed similar irritation to dithranol and 10-propionyl dithranol, and a third only to dithranol.

Group II. The initial mean thickness of the psoriasis plaques was 2.4 units in the 8 patients treated with different concentrations of dithranol (2 mmol), 10-propionyl dithranol (4 mmol) and 10-butyryl dithranol (8 mmol).

Irrespective of the concentration differences, the treated sites thinned within 20 days to a mean level of 0.5 (Fig. 3). White petrolatum alone caused a thinning to the level of 1.7.

The mean top-readings of staining in this group were 1.7, 1.4 and 1.5 for 10-butyryl dithranol, 10-propionyl dithranol and dithranol, respectively. One of the patients showed some irritation to all three hydroxyanthrones throughout the treatment period. Most of them had some residual redness at the treated sites.

DISCUSSION

In our experience, the use of Finn-chambers allows occlusive treatment of small confined skin areas and guarantees that the ointments remain exactly on the same site during the entire treatment period. Neither the part of the psoriasis lesion remaining uncovered by the chamber nor the other lesions under the tape showed any improvement during the 20 days of the trial. Because occlusion increases penetration, comparatively low concentrations of the hydroxyanthrones, corresponding to 0.05% dithranol, were used, and a clear antipsoriatic effect was attained within 20 days without undue adverse effects. If proper

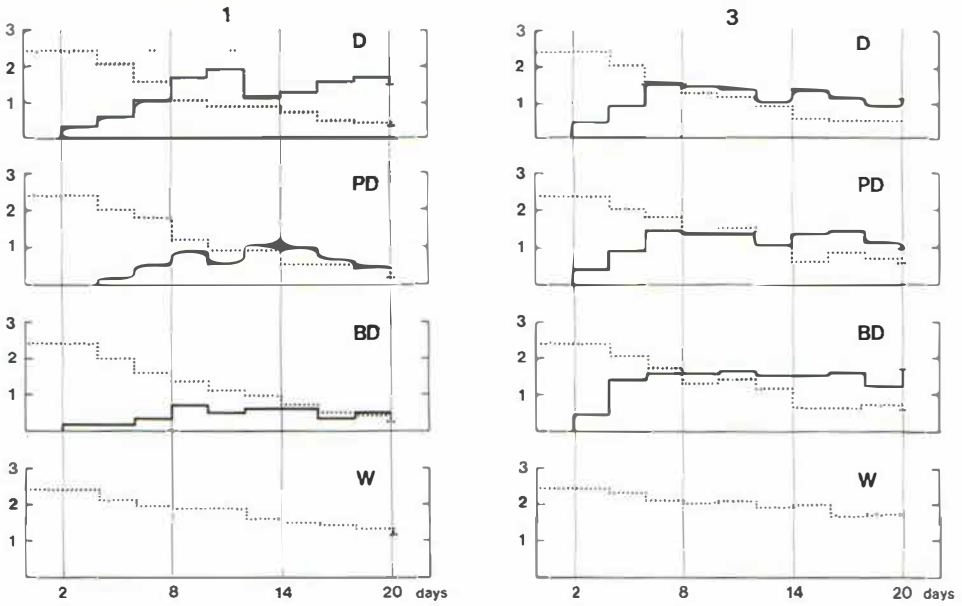

Fig. 1. The mean thickness (. . . .) and staining (——) of the psoriatic plaques on 9 patients during every 2nd-day-repeated application, when 2 mmol/kg concentrations of dithranol (D), 10-propionyl dithranol (PD) and 10-butyryl dithranol (BD) were used. Reading scales:

3 = thick plaque,
2 = plaque of medium thickness,
1 = thin plaque,
0 = no palpable lesion,

0 = no staining;
1 = brownish hue;
2 = reddish brown;
3 = dark brown.

Fig. 3. The mean thickness (. . . .) and staining (——) of the psoriatic plaques on 8 patients during every 2nd-day-repeated application, when 2 mmol/kg dithranol (D), 4 mmol/kg 10-propionyl dithranol (PD) and 8 mmol/kg 10-butyryl dithranol (BD) were used. Reading scales as in Fig. 1.

concentrations are used, the Finn-chamber technique would seem to be suited for early low-risk testing of new drugs on human skin. We agree with the suggestion that "candidates for therapeutic agents can be tested for efficacy on confined small areas of the skin in patients ... with a minimal risk of systemic or local adverse effects" (1).

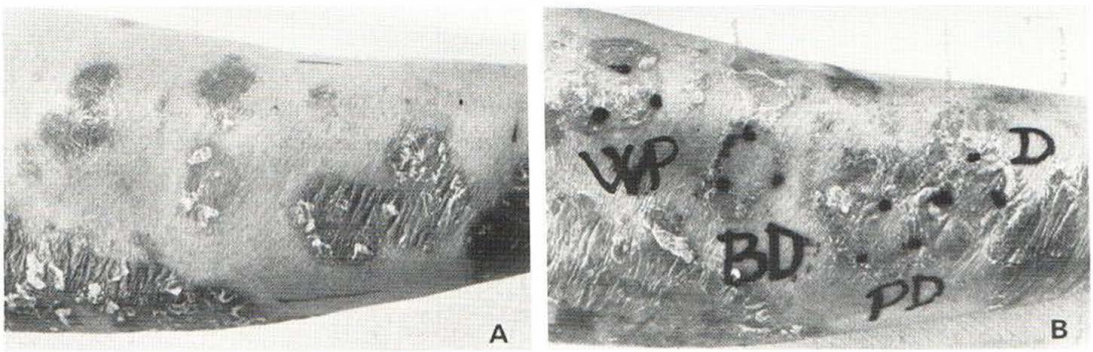

Fig. 2. An example of the antipsoriatic effect of dithranol (D), 10-propionyl dithranol (PD) and 10-butyryl dithranol (BD), all used in the concentration of 2 mmol/kg of white petrolatum. (A) Before treatment, (B) 12th day of treatment: the site treated with BD has already thinned away and regained normal skin colour.

Even if both treatment groups initially showed the same thickness of psoriasis lesions, the group treated with different concentrations of the three hydroxyanthrones consisted of more resistant patients, judging by the results obtained with dithranol and with white petrolatum alone. When equimolar (2 mmol) concentrations were used the three hydroxyanthrones showed the same antipsoriatic effect, but 10-butyryl dithranol was the least staining. With a four-fold concentration of 10-butyryl dithranol, almost the same antipsoriatic effect was obtained, but staining became intensified to the level caused by 2 mmol dithranol and by 4 mmol 10-propionyl dithranol. Thus in Phase II clinical trials it is advisable to use these hydroxyanthrones in equimolar concentrations.

Toxicological evaluations have revealed that of these three hydroxyanthrones, 10-butyryl dithranol was (1) least irritating in the mouse ear test, (2) best tolerated and least mutagenic for *S. typhimurium* strain TA 1537, (3) least damaging in the metaphase analysis of in vitro-treated human lymphocytes, and (4) non-tumour promoting in mouse skin (7). Therefore, 10-butyryl dithranol has been chosen for Phase II clinical trials to be conducted without occlusion using sticks based on paraffins (2). 10-butyryl dithranol has been approved as butantrone in the WHO nomenclature of non-proprietary drugs.

REFERENCES

1. Anonymous: Research needs in 11 major areas in dermatology. J Invest Dermatol 1979; 73: 402.
2. Brandt H, Mustakallio KK. Improved application of dithranol for ambulatory treatment of psoriasis. Psoriasis: Proceedings of the Third International Symposium (ed. Farber EM, Cox AJ. Grune & Stratton, New York, 1982; 385–386.
3. Brandt H, Mustakallio KK. Irritation and staining by dithranol (anthralin) and related compounds: III. Cumulative irritancy and staining during repeated chamber testing. Acta Derm Venereol (Stockh), 1983; 63: 237.
4. Mustakallio KK. Irritation and staining by dithranol (anthralin) and related compounds: I. Estimation with chamber testing and contact thermography. Acta Derm Venereol (Stockh) 1979; 59 (Suppl. 85): 125.
5. Mustakallio KK. Irritation and staining by dithranol (anthralin) and related compounds: II. Structure–activity relationships among 10-mesosubstituted analogues. Acta Derm Venereol (Stockh) 1980; 60: 169.
6. Mustakallio KK, Brandt H. Properties of some 10-acyl analogs of dithranol (anthralin). Psoriasis: Proceedings of the Third International Symposium (ed. Farber EM, Cox AJ). Grune & Stratton, New York, 1982; 379–380.
7. Mustakallio KK, Brandt H, Halmekoski J, Vilvala R, Martinmaa J, Honkanen E, Pippuri A, Haarala J, Männistö P. Structure–activity relationships among dithranol and its new derivatives. Poster presented in the 16th International Congress of Dermatology, Tokyo, 1982.
8. Pirilä V. Chamber test versus patch test for epicutaneous testing. Contact Dermatitis 1975; 1: 48.