

Irritation and Staining by Dithranol (Anthralin) and Related Compounds

V. Short-Contact and Tape-Stripping Experiments with Dithranol and Butantrone

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Dithranol (D) and butantrone (BD) were compared as regards irritation and staining in conditions resembling short-contact therapy. Nine psoriatics were tested with 0.5% D and 0.66% BD using exposures of 20 min and 3 h. Partial removal of the horny layer by 15 tape strippings *before* and *after* the exposure resembled the impaired barrier of lesions and post-treatment washing, respectively. Development of erythema and staining, and alterations in blood flow were followed for 7 days. In the unstripped skin, D caused after 20 min exposure within 3 days a faint but defined erythema and increase in blood flow, and within 7 days a brownish hue. Irritation was suppressed by stripping after 20 min exposure. After 3 h contact, irrespective of stripping, much stronger irritation and staining developed. BD caused no staining after 20 min of exposure and little if any erythema. After 3 h contact, it caused only minimal staining and markedly less irritation than equimolar D. *Key words:* Psoriasis; Dithranol; Anthralin; 10-butyryl dithranol; Butantrone; Short-contact therapy; Erythema; Skin blood flow. (Received March 22, 1983.)

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In the ambulatory treatment of psoriasis, dithranol (anthralin) may be tolerated in concentrations higher than 0.25% when the contact time is shortened to one hour (1) or less (2). When the skin is thoroughly washed with a neutral soap immediately after each exposure, irritation and staining of the perilesional skin should be reduced.

For this kind of "short-contact therapy", butantrone, 10-butyryl dithranol, could be even better than dithranol, because during 3 weeks of repeated 48-hour exposures of equimolar concentrations, butantrone stained less and was at most one-fourth as irritating (3) and its equal in antipsoriatic activity (4). Before starting short-contact therapeutic trials with butantrone and dithranol, we decided to compare irritation and staining responses of uninvolved skin to exposures shorter than 24 h. In addition, partial removal of the horny layer both before and after the exposures was used to mimic lesional skin and post-treatment washing, respectively.

MATERIAL AND METHODS

Nine unselected in-patients with plaque psoriasis were tested on uninvolved back skin with (1) 0.5% Dithrocream® (DC) (obtained from Dermal Laboratories Ltd.), (2) 0.5% dithranol in white petrolatum (DP), and (3) 0.66% butantrone in white petrolatum (BD), equimolar with 0.5% dithranol. For testing, Finn chambers 8 mm in diameter were used as described elsewhere (5), but instead of the 24-h contact time two shorter exposures, i.e. 20 min and 3 h, were used. To accomplish removal of the upper half (6) or at least one-third (7) of the horny layer, stripping with Scotch Tape 810 was repeated 15 times. The tests were applied on three comparable sites: one non-stripped, one stripped before exposure and

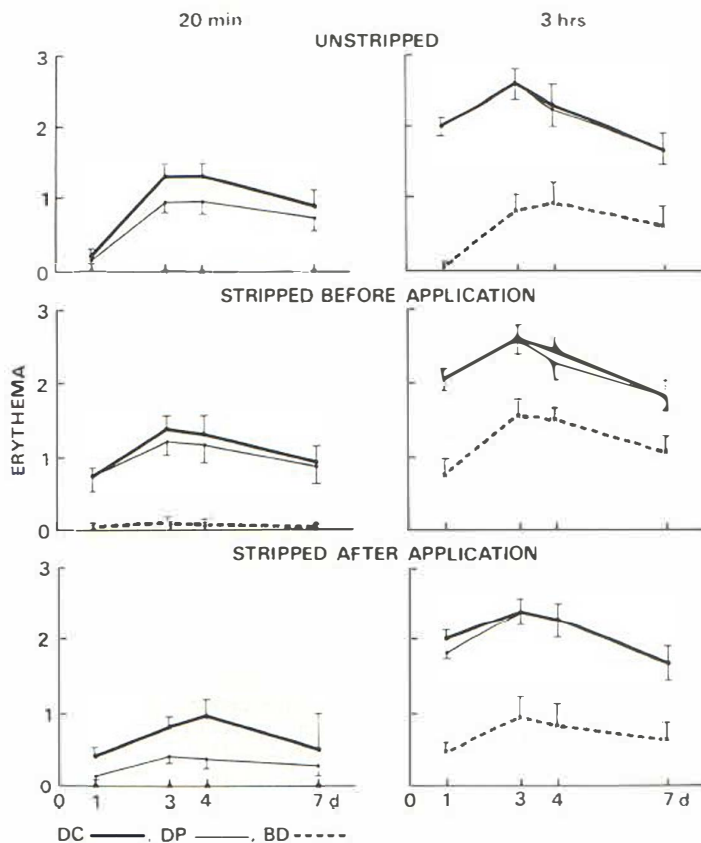


Fig. 1. Course of erythema during 7 days after 20-min and 3-h contact with 0.5% dithranol and 0.66% butantrone. DC = Dithrocream; DP = dithranol in petrolatum; BD = butantrone in petrolatum.

one after exposure. The site stripped before exposure resembles the enhanced penetration of psoriatic lesions, because a parakeratocytically altered horny layer corresponds approximately to incompletely stripped skin in barrier function (8). Partial stripping after exposure resembles the thorough washing needed in the short-contact therapy.

The readings of erythema plus staining and the measurements of superficial blood flow were made independently by two experienced observers using methods previously described (9). Visual estimation of erythema and staining was performed 1, 3, 4 and 7 days after application of the tests. Shortly thereafter on each day, laser Doppler flow measurements were made without knowledge of the visual estimates.

RESULTS

Fig. 1, 2 and 3 illustrate the results after 20 min and 3 h contact times.

20-min contact. In general, 0.5% Dithrocream (DC) elicited stronger erythema responses than 0.5% dithranol in white petrolatum (DP) (Fig. 1). This difference was most marked in sites stripped after exposure, even if these erythema responses were the weakest. The fastest appearance of erythema was seen in sites stripped before application. Practically no erythema was produced by 0.66% butantrone (BD): only in sites stripped before application did a hardly discernible threshold erythema (reading 0.25) develop in 2 of the 9 patients, and in one patient a faint ill-defined erythema (reading 0.5) was observed. **Blood flow** of the skin followed, in general, the course of erythema. However, stripping increased the first day blood flow, especially at sites stripped before application (Fig. 2). BD caused practically no increase in blood flow at the non-stripped sites. Little if any

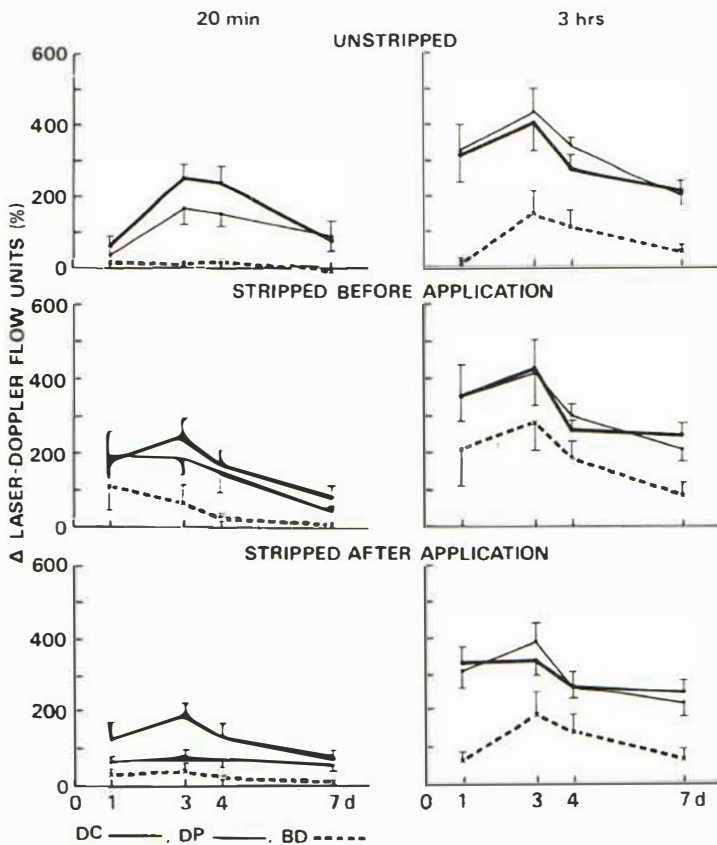


Fig. 2. Alterations in superficial blood flow during 7 days after 20-min and 3-h contact with 0.5% dithranol (DC and DP) and 0.66% butantrone (BD).

staining developed within 7 days when DC and DP were applied. BD caused no staining at all (fig. 3).

3-h contact. Erythema was markedly more pronounced after a 3-h contact than after a 20-min exposure (Fig. 1). Irrespective of stripping, the responses to DC and DP were practically identical and much stronger than erythema reactions caused by BD. The BD reactions, on the other hand, were more marked after stripping, especially at sites stripped before application. Blood flow of the skin followed rather closely the course of erythema except in the fourth-day measurements which were proportionately lower than the corresponding erythema readings (Fig. 2).

DP tended to increase blood flow more than DC, in contrast to the responses after 20 min contact time. BD did not increase blood flow as much as DP and DC. This difference was most marked in the non-stripped sites. In the stripped sites, especially in those stripped before application, BD caused an increase in the first-day measurements of blood flow. Staining of the skin caused by 3-h contact of both DC and DP was markedly more pronounced than after the 20-min exposure. It followed an almost identical, linearly increasing course during the 7-day observation period (Fig 3). In contrast, BD produced little if any staining.

DISCUSSION

When dithranol in petrolatum is applied to normal human skin, the epidermal concentration of the drug is dose dependent and increases with time, reaching a steady state after

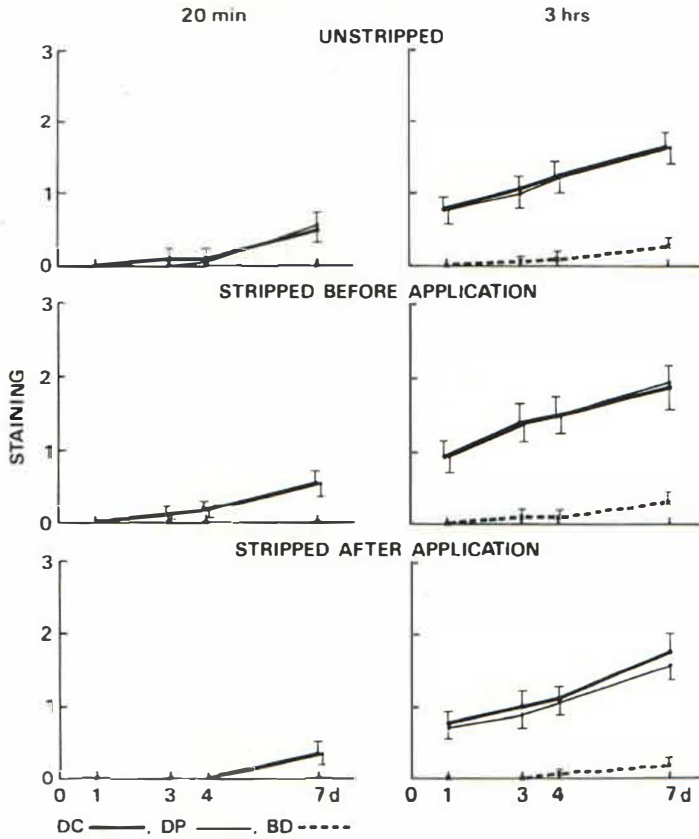


Fig. 3. Course of skin staining during 7 days after 20-min and 3-h contact with 0.5% dithranol (DC and DP) and 0.66% butantrone (BD)

some hours (10). For instance, when 1% dithranol is used instead of 0.1%, the epidermal concentration is increased by a factor of ten. Also the removal of the horny layer, mimicking the disturbed barrier function in psoriatic lesions, is followed by an increase by a factor of about ten for both concentrations of dithranol, and a steady state of penetration is reached within only one hour.

When dithranol is used in high concentrations ranging from 0.5% to 3%, it is advisable to limit the penetration process by shortening the contact time to 1 h (1) or even to 20 or 10 min (2). Because of the slower penetration into normal skin, the amount absorbed perilesionally could still be subthreshold in terms of irritation and staining, whereas therapeutic drug concentrations in the psoriatic plaque are already attained.

In the present study, 0.5% dithranol caused after a 20-min contact within 3 days a faint but defined erythema in the unstripped uninvolved skin of psoriatic patients. In the paraffin-cremor base, dithranol appeared to cause somewhat stronger erythema reactions than in white petrolatum, perhaps because of a difference in the early penetration of dithranol in these two vehicles. This difference was no longer present after a 3-h contact, which, irrespective of vehicle, resulted within 3 days in marked erythema reactions. The same can be deduced from the alterations of superficial blood flow, another parameter of skin irritation following quite closely the course of erythema reactions (9).

When one-third to one-half of the horny layer was removed by 15 strippings *before* application of dithranol, a situation approaching the penetration conditions of psoriatic lesions (8), the course of erythema reaction after 20 min contact time was initially faster

but later almost the same as at the unstripped sites. On the other hand, 15 strippings *after* 20 min exposure of dithranol, mimicking washing, caused less erythema, especially when white petrolatum was used as the vehicle. Applied under everyday conditions, this emphasizes the importance of washing immediately after the 20-min contact time.

In contrast, after a 3-h contact, similar erythema responses were obtained irrespective of stripping. Apparently, when the 0.5% concentration of dithranol is used, a tissue level of the drug causing marked irritation within 3 days is reached already during the 3-h contact period, obviously too long an exposure for short-contact therapy (2).

In general, *staining* of the skin due to 0.5% dithranol was much weaker after 20 min exposure than after 3 h contact, and there was little if any difference between staining caused by DC and DP. Even in terms of staining, it is advisable to use 20 min contact time in therapeutic trials, since only a brownish hue at the tested sites was noticeable after 7 days. In contrast, after a 3 h contact, 0.5% dithranol caused within 7 days a reddish brown staining similar to that produced by 0.2% dithranol after a 24 h exposure (9).

When butantrone and dithranol were compared regarding the side effects staining and irritation, butantrone was found superior, irrespective of contact time or stripping. After a 20-min contact, butantrone caused no staining at the tested sites, whether unstripped or stripped, before or after application and even after a 3-h exposure, staining was minimal. After 20 min of contact, irritation was minimal and a scarcely visible erythema reaction was seen only in a few patients at the sites stripped before application. Neither was the superficial blood flow increased at the unstripped sites, but stripping, especially before application, caused a transient stimulation of blood flow. In part, this may be due to the stripping itself, as the sites treated with dithranol also showed a similar reaction, though in this case noticeable also as a faster erythema response. After 3 h contact, butantrone caused a faint-to-slight erythema within 3 days, the sites stripped before application displaying an irritation sooner and more strongly also in terms of superficial blood flow.

These differences could be explained if butantrone were to penetrate the horny layer more slowly than dithranol. However, butantrone and dithranol show similar corneal penetration profiles (unpublished observations). Moreover, the phase I clinical trial published recently (4) revealed that butantrone and dithranol, when used in equimolar concentrations, are equivalent in antipsoriatic activity. Therefore, butantrone, as a less irritating, less staining and less toxic (4) derivative of dithranol, could be ideal for short-contact therapy of psoriasis.

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