Acta Derm Venereol (Stockh) 1998; 78: 262–265

Skin Irritation by Dithranol Cream

A Blind Study to Assess the Role of the Cream Formulation

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In connection with a national cost-effective evaluation study of short contact dithranol therapy for psoriasis, the question arose whether dithranol cream irritation is influenced by constituents of the vehicle. To establish the role of the different components of the vehicle in the mechanism of dithranol irritation, the dithranol 3% cream used in the evaluation study and its vehicle with nine different combinations of its components were tested in a blind study. The creams were applied for 15, 30 and 45 min on the backs of 12 healthy volunteers. Irritation was scored as erythema by visual and colorimeter scoring. The dithranol creams with salicylic acid among their stabilizers showed 42% more irritation than the dithranol creams with only sorbic acid or no stabilizers at all. Stability tests showed no significant degradation of dithranol in the two less irritating creams when kept at 4°C for 11 months. Salicylic acid in the cream aggravates dithranol-induced erythema. *Key words: anthralin; erythema; stabilizers; vehicle.*

(Accepted January 5, 1998.)

Acta Derm Venereol (Stockh) 1998; 78: 262–265.

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Dithranol (1,8-dihydroxy-9-anthrone), also known as cignolin or anthralin, has been used as an anti-psoriatic drug since 1916. Its anti-psoriatic and related irritative effect is caused by oxygen radical formation during auto-oxidation (1, 2). Dithranol disintegrates into danthrone and various dimers. Its decomposition is catalyzed by light, air, oxygen, water, high pH, and high temperature. The breakdown products have no effect on psoriasis, but are related to dithranol staining (3, 4). Dithranol irritation varies widely between individuals and between different parts of the body. The axilla, scrotum, breasts and the inside of the thighs are the most sensitive parts (5–7). Dithranol irritation on the non-affected skin can be diminished by shortening the dithranol contact time to between 10 and 45 min, without loss of clinical efficacy (7–9). Different ointments, sticks and creams have been developed for this short-contact treatment. We are using dithranol cream because it is easy to apply and to wash off. The dithranol concentration varies from 0.1% to 5.0%. The cream is applied for 15 to 45 min and washed off with water. Five years of experience showed that dithranol cream applied in this way sometimes irritates even more than dithranol in a fatty basis or paste, applied overnight or for 24 h, with comparable clinical efficacy. Therefore, the question arose whether the irritation is influenced by constituents of the vehicle. To establish the role of the different components of the vehicle in dithranol irritation, the dithranol 3% cream used in the evaluation study and its vehicle with 9 different combinations of its components were tested in a blind manner on 12 healthy volunteers.

MATERIAL AND METHODS

Subjects

After having given written informed consent, 12 healthy Caucasian volunteers (5 males, 7 females, aged 23–28 years), without signs or history of skin disease, were tested on their backs. Because of the controversial role in dithranol irritation the subjects did not use anti-inflammatory agents such as antihistamines, NSAIDs or corticosteroids from 1 month prior to the test until after the test (5, 10). Approval for the study had been obtained from the hospital ethics committee.

Test substances

The test substances consisted of the 3% dithranol cream and of nine different combinations of the components of the cream with and without dithranol 3% (Tables I and II). The creams were prepared by the hospital pharmacy, and coded 1 to 10. The test creams with dithranol were freshly prepared 1 day prior to the test and were controlled for their dithranol concentration on the test day itself. The stability of the less irritating dithranol containing creams (2 and 3), kept at 4°C in aluminum coated tubes, was tested. The stability was 100% after 4 months and 95% after 11 months.

Exposure

On the back of each subject three columns of 10 marked test sites (columns I –III), were situated on the left, middle and right side of the back, respectively. Of each test substance 0.05 ml was applied in the centre of these test sites (diameter 2.5 cm) and spread carefully and equally within the site using a fresh finger condome for every application. Each substance was applied once, in every column. To avoid the influence of site variation in irritation on the back, applications were performed according to the Latin square principle. Intraindividually the creams in columns I, II and III were distributed similarly. Creams in columns I, II and III were left in place for 15, 30 and 45 min, respectively. To avoid the influence of the side of the back (right, middle or left), times of exposure of columns I, II and III varied interindividually. To avoid irritation other than dithranol-induced irritation, the creams were removed with tapwater only. All evaluations were performed by one examiner, who did not know the application and exposure scheme used. The creams were applied and washed off by someone else.

Visual scoring

Thirty minutes and 8, 24, 48 and 72 h after removal of the creams, all 30 test sites were evaluated. Visual scoring was performed for the

Table I. *Formulation of dithranol cream 3% as used in day-care centres*

Dithranol	30 g
Vehicle	
Cetiol V	230 g
Cetomacrogol emulsifying wax	150 g
Liquid paraffin (viscosity 110–230 mPa.s.)	150 g
Stabilizers	
Sorbic acid	1.5 g (0.15%)
Ascorbic acid	0.5 g (0.05%)
Salicylic acid pulv < 90	10 g (1.0%)
Distilled water	Up to 1.0 kg

 ISSN 0001-5555

Table II. *Test creams, numbered 1 to 10, as prepared by the hospital pharmacy*

1.	Dithranol 3%, vehicle, sorbic acid, ascorbic acid, salicylic acid
2.	Dithranol 3%, vehicle
3.	Dithranol 3%, vehicle, sorbic acid
4.	Dithranol 3%, vehicle, ascorbic acid
5.	Dithranol 3%, vehicle, salicylic acid
6.	Vehicle, sorbic acid
7.	Vehicle, ascorbic acid
8.	Vehicle, salicylic acid
9.	Vehicle, sorbic acid, ascorbic acid, salicylic acid
10.	Vehicle

appearance of erythema and oedema, vesicles and pustules. Itching or pain was also noted. The erythema and oedema score has been used earlier in another dithranol irritation study (11) and consisted of: no erythema = 0, hardly perceptible redness = 1, weak but definite erythema = 2, marked erythema = 3, marked erythema with minimal oedema = 4 and marked erythema with marked oedema = 5. For visual scoring the central part of the test sites was scored, corresponding to an area scored by the colorimeter. The scoring for itching and pain was classified as: none = 0, slight = 1 and evident = 2.

Colorimetric scoring

Colorimetric quantification of erythema has been used in the past for erythema induced by UV light, sodium-lauryl sulphate and dithranol 3% (11–13). We used a Minolta tri-stimulus colorimeter, model CR-200. This meter contains a probe consisting of a 4-cm perspex plate with a central opening of 11 mm through which flashes of natural daylight from a xenon lamp are sent towards the skin. The skin-reflected light is analysed by silicone photo cells. Every measurement is composed of three consecutive light flashes. Using this method, erythema is expressed in an objective measure, which correlates positively with clinical scoring of erythema (12, 13). According to the guidelines for measurement of skin colour and erythema (14), all test sites were left uncovered and motionless for at least 5 min prior to the measurements. Subjects were placed in a standardized position and room temperature was between 19 and 23°C. Direct sunlight was prevented. The meter was calibrated according to the manufacturer's instructions and a baseline colour analysis was performed for each subject on all 30 untreated, non-dithranol-exposed test sites on the first day of the test. The treated sites were expressed against the subject's own baseline standard.

Dithranol concentration

The dithranol concentrations in the creams were measured after extraction using a straight-phase High Pressure Liquid Chromatographic (HPLC) method (15). The measurements were carried out at room temperature. The conditions were briefly as follows: extraction fluids: dichloromethane, n-hexane; internal standard: 1 g 2-nitroaniline in 10 ml methanol; chromatograph: P1000 isocratic pump, AS 1000 autosampler, SCM 400 solvent conditioner, and UV 1000 detector (Thermo Separation Products); column: Lichrosorb SI 60–5-L, 15 cm (4.6 mm I.D.) (Chrompack 28802); detection wavelength: 354 nm; integrator: ChromJet 4400 (Thermo Separation Products); mobile phase: dichloromethane + n-hexane + glacial acetic acid (5 + 82 + 1); flow rate: 2 ml/min and injection volume: 20 µl.

Statistics

Data were statistically analysed using the Tukey Studentized Range (HSD) test and the General Linear Models Procedure. Correlation of the visual score and the colorimetric values were calculated with the Spearman's rank test ($\alpha = 0.05$).

RESULTS

Visual scoring

Overall 360 test sites (12 subjects × 3 rows × 10 test substances) were evaluated.

Long-lasting erythema appeared at t = 24 h in all 180 test sites exposed to a cream containing dithranol. We did not observe oedema. Dithranol brown staining occurred in seven subjects and showed a high interindividual variability in intensity. There was no correlation between the grade of brown-colouration and the cream number used on the stained test site. In 73 of the 360 test sites (20.2%), a transient erythema appeared 30 min after removal of the creams 1, 3, 6 and 9. In 15 test sites (4.1%) it appeared as a central redness, and in 58 test sites (16.1%) as an erythemal ring on the rim. This erythema had disappeared at t = 8 h. There were no vesicular reactions. Two subjects developed a slight pustular reaction after 72 h, both on two different test sites which were exposed to a dithranol-containing cream (creams 2, 3 and 5). Slight pain reported in four subjects was transient and independent of the exposure time, the cream number or the test site. Slight itching was noted in five subjects, especially on test sites of creams 3, 4 and 5.

Colorimetric scoring

Colorimetric evaluation of the sites before application of the creams showed an interindividual variability. To eliminate the influence of this variability, all colorimetric values were assessed against the patients' own baseline measurements. At t = 8 h the colorimeter showed a clear rise on sites treated with creams 1 to 5 and a small rise on sites with creams 6 to 10. The mean erythema score for creams 1 to 5 showed a rising tendency up to 72 h. Creams 6 to 10 showed no significant changes in erythema scores. In the 180 dithranol-exposed test sites, 49 times (27.2%) the erythema maximum was reached after 48 h and 131 times (72.3%) the erythema scores were rising up to 72 h. The mean colorimetric erythema scores of the sites with brown-staining showed no significant difference from the mean scores of the sites without dithranol staining. Apparently this did not influence our colorimetric measurements.

The mean maximum score for erythema was found at 72 h. Erythema values showed no significant difference between 15, 30 or 45 min of exposure, so the measurements of all exposure times together were used for evaluation. The visual and colorimetric scores showed a significant correlation as expressed by the median Spearman Rank Correlation Coefficient of 0.75 (range 0.47–0.90). The colorimetric results at 72 h were used for statistical analysis. A significant difference in erythema score was found between creams 1 and 5 compared to creams 2 and 3. Creams 1 and 5 showed a mean erythema score at 72 h of 4.92; creams 2 and 3 reached only 2.88, which is 42% less. Cream 4 showed an intermediate reaction (Fig. 1). None of the creams without dithranol (creams 6 to 10) elicited erythema or other signs of irritation, except for the transient visually scored erythema at t = 30 min, as mentioned above.

Dithranol concentration

All dithranol-containing creams complied with the British Pharmacopoeia requirements (15). When kept at 4°C in aluminium-coated tubes for 11 months, the dithranol concentration

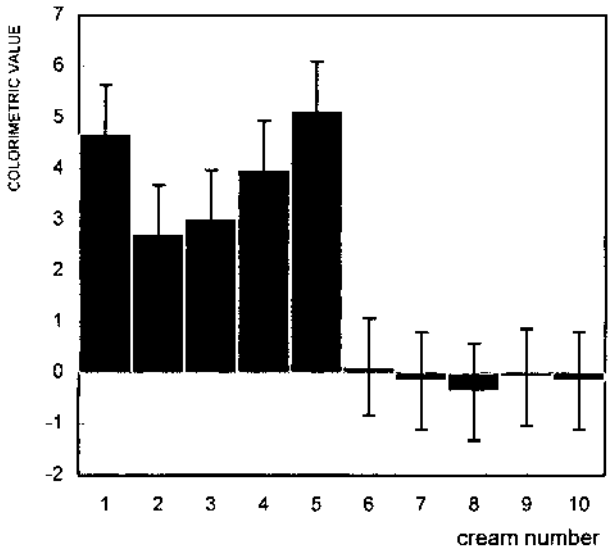

Fig. 1. Mean colorimetric erythema values of 12 subjects (±SD), adjusted to their own baseline values, 72 h after removal of the creams.

in the less irritant creams (2 and 3) was still within the accepted range.

DISCUSSION

The normal skin of psoriatic and non-psoriatic individuals shows no difference in reaction to dithranol, nor is there any association with age, gender or skin type and original skin thickness (6). The higher erythema score of dithranol from an oil-in-water emulsion compared to more lipophilic bases might be caused by a significantly faster release of dithranol from a cream, as shown *in vitro* (16). However, dithranol penetrates best from more hydrophobic ointments, which was shown *in vivo* with tritium-labelled dithranol (17, 18). Dithranol erythema is dose-dependent, with a higher dose giving an earlier and more severe reaction (5, 19). A concentration of >1% dithranol can elicit pustular reactions, which we observed in two subjects (7). In agreement with earlier reports, long-lasting erythema occurred 24 h after dithranol exposure and reached its maximum in both visual and colorimetric scores at 48–72 h (1, 11, 20, 21). The transient early erythema was not detected by the colorimeter, probably because it concerned a ring of redness in most cases, which was not seen by the 11 mm wide "eye" of the colorimeter. Because the transient redness was localized centrally in only 15 of the 360 test sites this did not influence the measurements significantly. This erythema was probably provoked by sorbic acid, which we add to our cream as a preservative in a concentration of 0.15%. This is described to exert a transient erythema appearing within 20 min after application (22). Dithranol from a hydrophilic ointment penetrates in a small but constant amount into the epidermis and shows only little difference in epidermal penetration after 10 and 30 min of exposure (17). This might be the explanation why we did not observe a significant difference in erythema scores at different exposure times.

Besides dithranol 3% and the vehicle, salicylic acid was the corresponding ingredient in our most irritating creams (1 and 5), which implies that salicylic acid in our cream formulation promotes irritation. Our assay supports the assertion that salicylic acid by itself is not pro-inflammatory (cream 8) (6, 23, 24). Not much is known about the effect of salicylic acid on the clinical efficacy of dithranol therapy. Salicylic acid is described as promoting the release of dithranol from a cream and enhancing skin penetration (1, 17, 25). This implies that the irritation we saw was caused by a higher skin concentration of dithranol. On the other hand not all authors confirm an enhanced skin penetration by salicylic acid (24, 26). It might be that the salicylic acid influences the dithranol irritation itself by a so far unknown mechanism, without influencing the penetration of dithranol. If the latter statement is true, a cream without salicylic acid would irritate less. This could lead to a quicker rise in dithranol cream concentration during treatment and a higher clinical efficacy.

In water-based dithranol formulations, oxygen dissolved in water oxidizes the dithranol and causes loss of activity (3). Stabilizers, such as ascorbic acid and salicylic acid, are added in a cream base formulation to prevent or delay this oxidation (27). This stabilizing function of salicylic acid in dithranol cream is in dispute, some authors even state that salicylic acid in a cream would diminish its stability (1, 28–30). Salicylic acid is also added as a preservative to dithranol in white petrolatum or pasta Lassar, in which it does not lead to increased irritation, so possibly also the vehicle base plays a role in the mechanism of enhanced irritation in dithranol cream. It has to be borne in mind that we used a 3% dithranol cream, which disintegrates much more slowly and irritates much more quickly than a dithranol cream of a lower concentration. Further study is needed to establish the irritant potential, the dithranol stability and the clinical efficacy of a cream with a lower concentration of dithranol with and without salicylic acid as a stabilizer.

ACKNOWLEDGEMENTS

We thank M. Beelen (chemical analyst) for skilfully carrying out the dithranol analyses and A. van Mameren (pharmacy technician) for her contribution in preparing the different creams.

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