The Effect of Clobetasol-17-propionate and Crude Coal Tar on Dithranol-induced Inflammation

A Clinical and Biochemical Study

P. C. M. VAN DE KERKHOF and M. G. H. TIMMERMAN

Department of Dermatology, University of Nijmegen, The Netherlands

Clobetasol-17-propionate (CP) and crude coal tar (CT) have an anti-inflammatory potential. Both agents have been advocated to suppress irritation of the skin during dithranol treatment. The effect of CP and CT on dithranol-induced irritation was studied by the assessment of erythema and measurement of alkaline phosphatase (ALP) as a direct reflection of the metabolic activity of the endothelial cells. Dithranol was applied for 2 h in the relatively high concentration of 10%, which resulted in a marked inflammation of the skin in all volunteers. Neither CP nor CT influenced the erythema. In contrast, CP and CT had a synergistic effect on the dithranol-induced induction of ALP. In conclusion, the present study indicates that CP and CT are not indicated for the treatment of dithranol-induced irritation.

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P. C. M. van de Kerkhof, Department of Dermatology, University of Nijmegen, Javastraat 104, 6524 MJ Nijmegen, The Netherlands.

Dithranol is an effective and safe remedy for chronic plaque psoriasis. However, irritation of the skin induced by this treatment necessitates careful supervision.

Topical corticosteroids have been reported to inhibit dithranol irritation (1–4), but in several studies such an action of corticosteroids was not confirmed (5, 6).

Recently the addition of coal tar to dithranol has become a popular combination. The clinical efficacy of the combination has been reported to be similar to that of dithranol monotherapy, whereas the irritation of the combination proved to be much less than that of dithranol monotherapy (7–11). It has been suggested that this effect is caused by the inactivation of dithranol by coal tar (12, 13). So far, any biological effect of coal tar on dithranol inflammation remains unsubstantiated.

ALP is a marker for the capillary involvement in the process of inflammation (14–16). In a previous study it was shown that ALP is a useful marker for the quantification of dithranol-induced inflammation (17).

In the present study the effect of CP and CT was assessed on inflammation induced by 2 h applications of dithranol in the relatively high concentration of 10%. Inflammation was quantified by using ALP as a marker enzyme.

MATERIALS AND METHODS

Subjects

Altogether 12 healthy volunteers (8 women and 4 males, aged 18–31 years) participated in this study. None had any sign or history of skin disease.

Application of ointments

The ointments were applied on three marked test areas (diameter 2 cm) on the upper arms. Following the application of the ointments, test areas were covered with permeable gauze. The application schedule of ointments is summarized in Table I.

In 6 volunteers, dithranol-induced inflammation was measured following a 24-h pretreatment and a 3-day posttreatment with CP 0.05% in a cream base (Dermovate cream, Glaxo), or cream base only (skin base cream, Glaxo). On test areas 1 and 3, CP cream and on test area 2, the cream base only were applied 24 h and 10 h before the application of dithranol. After cleansing the skin with water and soap, dithranol 10% in petrolatum was applied on areas 1 and 2 and petrolatum only was applied on area 3. After an application period of 2 h, dithranol and petrolatum were removed with arachis oil, water and soap. Test areas pretreated with CP cream (areas 1 and 3) were treated twice daily with CP cream for 3 days. The test area pretreated with cream base only was post-treated for 3 days twice daily with this cream.

In 6 volunteers, dithranol-induced inflammation was measured following a 24-h pretreatment and a 3-day posttreatment with CT 5% in petrolatum resp. petrolatum only. On test areas 1 and 3, CT in petrolatum and on test area 2, petrolatum only were applied 24 h and 10 h before the application of dithranol. After cleansing the skin with arachis oil, water and soap, dithranol 10% in petrolatum was applied on test areas 1 and 2 and petrolatum only was applied on test area 3. After an application of 2 h, dithranol and petrolatum were removed with arachis oil, water and soap. Test areas pretreated with CT in petrolatum (areas 1 and 3) were post-treated twice daily with CT in petrolatum for 3 days. The test area pretreated with petrolatum only was post-treated with petrolatum twice daily for 3 days.

Clinical assessment and biopsy procedure

Erythema was assessed using a 4-point scale on days 1, 2, 3, 4 and 8 after the application of dithranol. On days 4 and 8, biopsies were taken from the three test sites, without anaesthesia using a razor blade in conjunction with a metal guard. In each subject one biopsy was taken from the untreated skin. Biopsies were rinsed in phosphate-buffered saline, dried with filter paper and weighed. Biopsies were processed immediately for measuring ALP activity.

Analytical procedures

Biopsies were homogenized in bovine serum albumin (1 mg/ml), using an all-glass Potter homogenizer. After centrifugation, ALP activity was measured as described previously (15, 16). In brief, samples of the supernatant (20 µl) were incubated with 20 µl of a solution containing 0.5 mM 4-methylumbelliferylphosphate and 5 mM NaF at pH 9.8. After 1 h at 37°C, 1 ml carbonate buffer (pH 10.5) was added and the release of 4-methylumbelliferone was determined fluorimetrically.

RESULTS

In all subjects, on all dithranol application sites, a marked erythema and a slight to moderate edema were seen with a maximum after 2 days. No blistering was observed in any of the subjects. Eight days after the application of dithranol, erythema had faded. Dithranol applications did not stain the skin. Fig. 1 illustrates the effect of treatment with CP and CT on dithranol-induced erythema. It can be seen that CP and CT did not affect the dithranol-induced erythema. CP and CT as monoapplication did not provoke any erythema.

ALP activity increased markedly following the dithranol applications. Fig. 2 demonstrates the effect of CP and CT on the ALP induction by dithranol. CP enhanced this induction of ALP markedly (on days 4 and 8; $p < 0.05$, Wilcoxon ranking test for paired data). CT also resulted in a pronounced enhancement of ALP induction by dithranol ($p < 0.05$ on days 4 and 8, Wilcoxon ranking test for paired

Table I. *Application schedule of ointments*

	CP and dithranol			CT and dithranol		
	Test area 1	Test area 2	Test area 3	Test area 1	Test area 2	Test area 3
Pretreatment	CP	Cream	CP	CT	Petrolatum	CT
Treatment	Dithranol	Dithranol	Petrolatum	Dithranol	Dithranol	Petrolatum
Posttreatment	CP	Cream	CP	CT	Petrolatum	CT

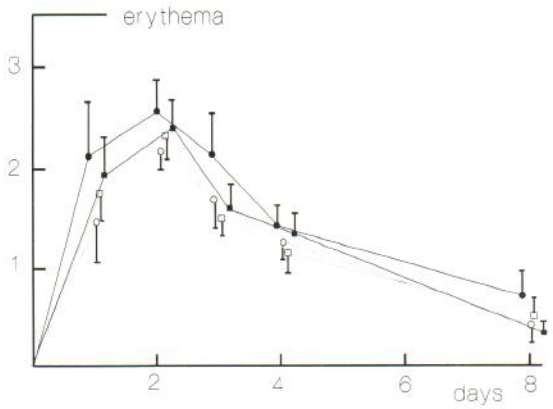

Fig. 1. Erythema scores (mean ± SE) following a 2-h application period of dithranol (10%) in petrolatum. ○, Cream base/dithranol; ●, clobetasol cream/dithranol; □, petrolatum/dithranol; ■, coal tar/dithranol.

data). Therapy with CP or CT alone did not modify ALP activity.

DISCUSSION

The inflammation resulting from dithranol application, has an acute phase with the release of mediators of inflammation. During the first 24 h prostaglandin E_2 (PGE_2) is released (18, 19). Edema of the skin coincides with maximum release of PGE_2 (20). At 48–72 h after the application of dithranol, PGE_2 levels have been reported to be normal and 12-hydroxyeicosatetraenoic acid (12-HETE) to show a maximum accumulation (18, 19). Vasodilatation coincides with the accumulation of 12-HETE. Assessment of erythema, skin contact temperature, laser Doppler flowmetry, had given maximum readings 48–96 h after the application of dithranol (21–23). Whereas these functional abnormalities had normalized after 7 days, the assessment of ALP activity revealed a biochemical abnormality of the capillaries which persisted as long as 15 days (17). The present study confirms the dynamics for erythema and ALP induction.

Although some clinical studies suggest that topical corticosteroids reduce the irritancy potential of dithranol during the treatment of plaque psoriasis (1, 4), studies using open patch tests on normal skin are not unequivocal. Topical corticosteroids have been reported to reduce edema resulting from dithranol application (1, 2). Erythema scores following dithranol application are not affected by corticosteroid treatment (6, 7). In the present study, CP resulted in an enhancement of the induction of ALP in the late phase of dithranol inflammation.

Several studies indicate that the addition of coal tar products to dithranol reduces dithranol-induced inflammation (7, 10, 11). Inactivation of dithranol by the addition of coal tar products has been reported. Such an inactivation proved to have a significant effect, especially on dithranol in low concentrations (13). If dithranol is applied over 24 h in low doses, pretreatment with coal tar products also inhibits the inflammation (8, 9). Again, inactivation of dithranol might well occur in this sequential combined therapy. The present study shows that CT augments the inflammatory action of 2 h applications of dithranol in petrolatum in a 10% concentration.

The assessment of erythema is semiquantitative. The quantification of ALP activity permits a more precise quantification of the biological effect. Therefore the increased dithranol-induced inflammation by adding CP and CT assessed by ALP might well remain below the sensitivity of the assessment of erythema.

Dithranol irritancy can be troublesome for the patient and limits this highly efficient antipsoriatic therapy. The present study demonstrated that corticosteroids and tar are not indicated for the treatment of irritation induced by high doses of dithranol.

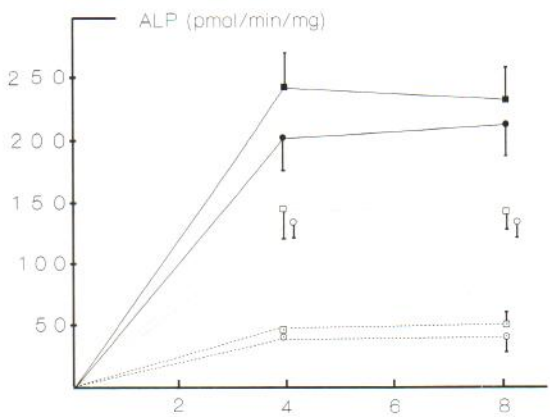

Fig. 2. Alkaline phosphatase activity (mean ± SE) following a 2-h application period of dithranol (10%) in petrolatum. ⊙, Clobetasol cream only; ○, cream base/dithranol; ●, clobetasol cream/dithranol; ⊡, coal tar only; □, petrolatum/dithranol; ■, coal tar/dithranol.

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