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ERYTHEMA CRAQUELÉ PROVOKED BY CORTICOSTEROIDS ON NORMAL SKIN

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Abstract. The provocation of erythema craquelé after cessation of long-term continuous steroid application to normal skin was investigated in 58 healthy subjects, usually under occlusion. No correlation was demonstrated between the erythema craquelé and skinfold thickness measured with the Harpenden technique.

Key words: Erythema craquelé; Corticosteroids; Hydrocortisone 17-butyrate; Betamethasone 17-valerate

Erythema craquelé (eczema craquelé, xerotic eczema) is a common skin reaction which develops in conditions of low humidity and presents as exaggerated chapping. It occurs most frequently during the dry cold weather of winter but may also be induced by air conditioning in summer. The reaction can be provoked and worsened by exposure to water, soap and detergents. It has been associated with myxoedema, lymphoma and zinc deficiency.

Topical corticosteroids applied to normal skin may induce a functional abnormality so that the site becomes vulnerable to desiccation and develops a severe erythema craquelé.

MATERIAL AND METHODS

Five studies involving topical applications of corticosteroids were undertaken in 58 healthy medical students and nurses with normal skin, from whom informed consent had been obtained, to study the phenomenon of erythema craquelé (Table I).

Studies 1–5 were also used to investigate the clinical effect of long-term topical corticosteroids on normal skin with regard to skinfold thinning. The 5th study was designed to investigate specifically the effect of betamethasone 17-valerate (Betnovate® Glaxo) and hydrocortisone 17-butyrate (Locoid® Gist-Brocades) without occlusion in those volunteers who previously experienced erythema craquelé with occlusion.

Betnovate® (betamethasone 17-valerate 0.1 %) cream, Locoid® (hydrocortisone 17-butyrate 0.1 %) cream and hydrocortisone 1% cream (ACO, Sweden) were used in their commercial formulations. The Locoid® cream base alone and varying concentrations of hydrocortisone 17-butyrate (0.03 %, 0.01 % and 0.003 %) in alcohol/pH 5 as well as alcohol/pH 5 alone were also used (Table I). Alcohol/pH 5 was necessary to maintain the stability of the hydrocortisone 17-butyrate.

Applications

In all the studies the various trial agents were applied according to a randomized double-blind code. On each volunteer, two identical sites were demarcated symmetrically on the ventral aspect of each forearm, using a rectangular stamp, 3 cm by 5 cm in size. To standardize the amounts applied, the creams were put on the skin as a thin line across the diagonal of the rectangle, using a thin-nozzled tube and in the case of solutions, three drops were delivered by a special dropper tube. The test substances were then spread evenly over the test areas.

Applications were made daily and the sites were covered with an occlusive plastic dressing which was kept in place until the following day, except in the case of the 5th study where two of the sites were kept unoccluded.

After removal of the dressing, the skin was inspected and skinfold thickness measurements were made at the defined intervals. The skin was then gently washed with water and soap and, after drying, a new application of the test material immediately followed.

Assessments

Immediately after removal of the plastic dressing during the daily changing of bandages, measurements of the skinfold thickness were performed with the Harpenden skinfold caliper (1, 2). On each occasion 10 readings were taken in each rectangle and the average expressed in mm was used in the calculations. The results of the measurements at the different times will be reported in a separate paper.

Both during the trial and for 2 weeks afterwards, the skin was inspected repeatedly with respect to morphological changes. The severity of inflammatory reactions, usually of the erythema craquelé type, was graded: absent, sligth/moderate, or marked.

Biopsies for histological examination were taken from 5 subjects with erythema craquelé.

Statistical methods

After careful checks had been made to ensure that the variances were homogeneous, parametrical statistical methods were used. Due to missing data, the scores from 4 subjects (3 from the 2nd and 1 from the 4th study) had to be excluded from the analyses but not from the estimation of the occurrence of erythema craquelé. Data on mean

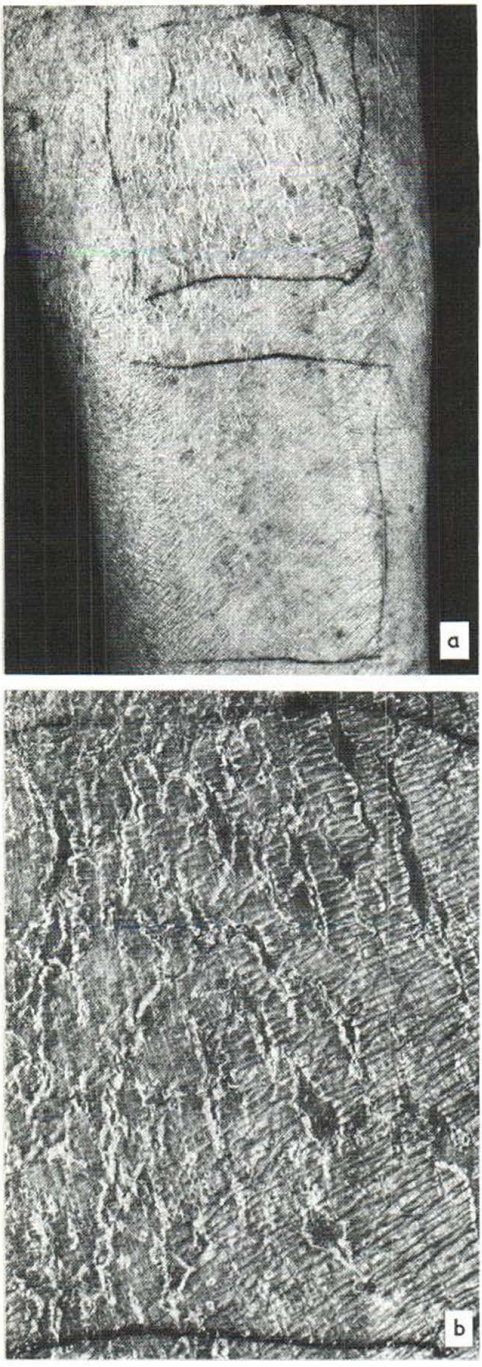

Fig. 1 a, b. Erythema craquelé provoked on normal skin by continuous occlusive treatment during 6 weeks with hydrocortisone 17-butyrate in ethanol 0.03 % (upper area) and 0.003 % (lower area). Apperance the day after finishing treatment.

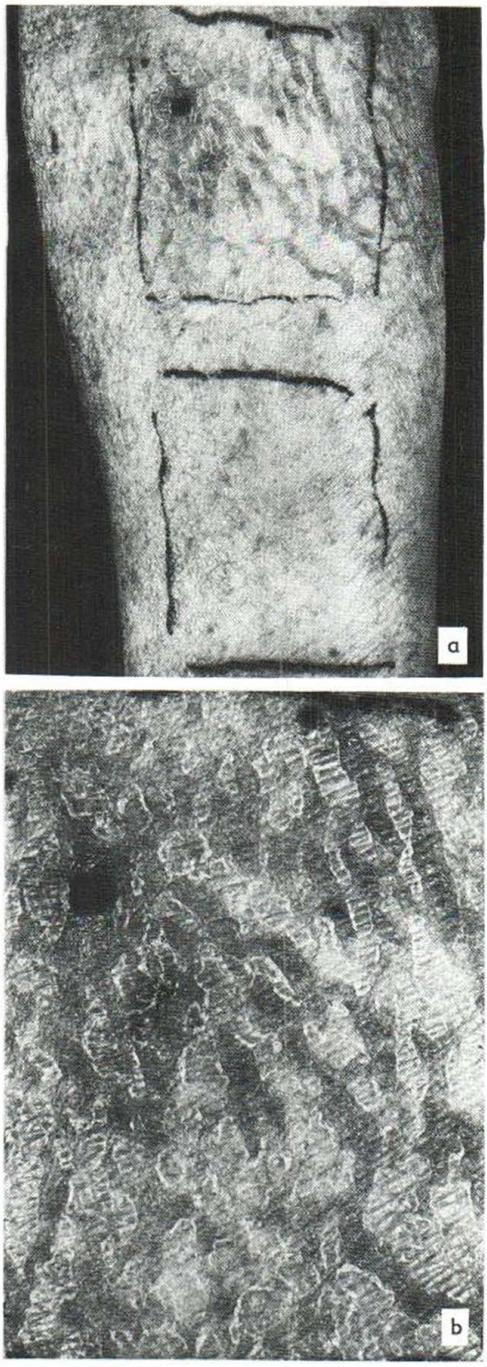

Fig. 2 a, b. Erythema craquelé provoked on normal skin by continuous occlusive treatment for 6 weeks with hydrocortisone 17-butyrate in ethanol 0.03 % (upper area) and 0.003 % (lower area). Appearance 4 days after finishing treatment.

Table 1.

Study no.	No. of subjects	Season of the year	Duration of daily application	Comparative preparations
I	12[a] (12)	Winter (Dec.–Jan.)	6 weeks	Betnovate 0.1% cream Locoid 0.1% cream
II	11[a] (7)	Spring (March–April)	9 days	Locoid 0.1% cream Hydrocortisone 1% cream Cream base Occlusion alone
III	10[a] (10)	Autumn (Sept.–Oct.)	6 weeks	Locoid 0.1% cream Hydrocortisone 1% cream Cream base Occlusion alone
IV	13[a] (12)	Winter (Jan.–Febr.)	4 weeks	Hydrocortisone 17-butyrate in ethanol pH 5 0.03%, 0.01%, 0.003% Ethanol pH 5 alone
V	12[a] (12)	Spring (March–April)	5 weeks	Betnovate 0.1% cream with occlusion without occlusion Locoid 0.1% cream with occlusion without occlusion

[a] Number of volunteers tested.
( ) Numbers analysed for effects on dermal thickness.

amounts of skin thinning, i.e. pre-treatment thickness minus thickness at time of maximum "atrophy" were examined for any correlation with the occurrence and different severities of erythema craquelé in 29 subjects treated with hydrocortisone 17-butyrate (Locoid®) cream and in 12 subjects exposed to the three different concentrations of hydrocortisone 17-butyrate solutions.

RESULTS

1. *Morphological changes at the test sites*

Where erythema craquelé was going to develop, it was observed that within approximately 12 hours of stopping treatment, the test areas became covered initially with a pattern of superficial fissuring of the skin, often with an inflammatory reaction. These narrow fissures widened during the next few days and ended up as diffuse erythema, some cases even having a papular quality to the reaction (Figs. 1, 2, 3, 4). In fact one woman had such an intense reaction that her entire forearms became swollen for a few days. Soreness and slight pain was often noticed at the height of the reactions. In the milder reactions the lesions settled in 3–4 days but with the more severe reactions the lesions peaked in about 5 days, thereafter gradually disappearing but occasionally persisting as a slight brownish discoloration up to 6 weeks after stopping therapy.

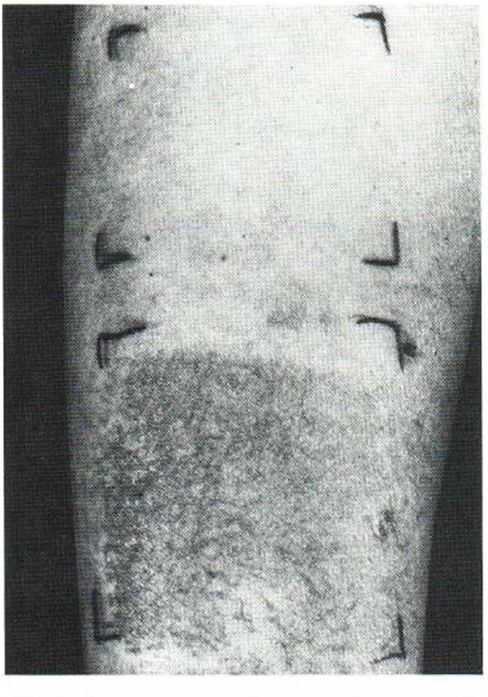

Fig. 3. Erythema craquelé provoked on normal skin by continuous treatment for 5 weeks with betamethasone 17-valerate 0.1% cream. Upper area without occlusion, lower area with occlusion. Appearance the day after finishing treatment.

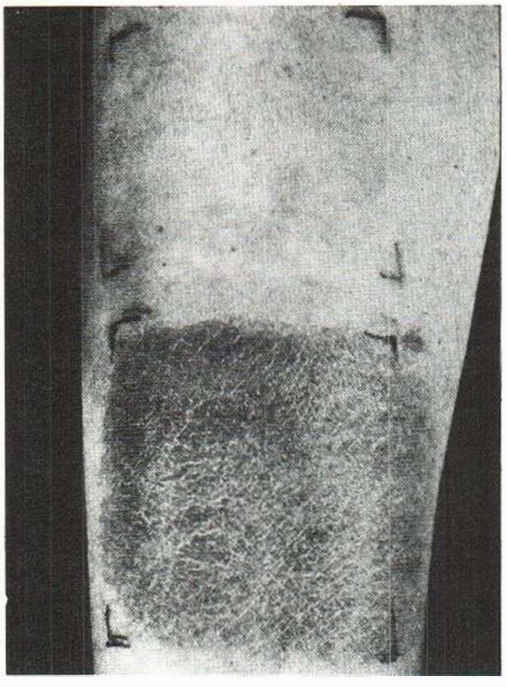

Fig. 4. Erythema craquelé provoked on normal skin by continuous treatment during 5 weeks with betamethasone 17-valerate 0.1% cream. Upper area without occlusion, lower area with occlusion. Appearance 7 days after finishing treatment.

In a few cases the erythema reactions also occurred outside the steroid application areas under the occlusive dressing. In these cases, however, the reaction was always more intense in the application areas. In one subject a slight reaction was provoked by the alcoholic solution alone.

Histology. In some biopsies the epidermis was extremely thin, with only a few layers of cells remaining (Fig. 5). In others "superficial haemorrhagic fissures of the skin" were observed with cracks through the epidermis down to the papillae of the dermis and a few erythrocytes in the fissures (Fig. 6).

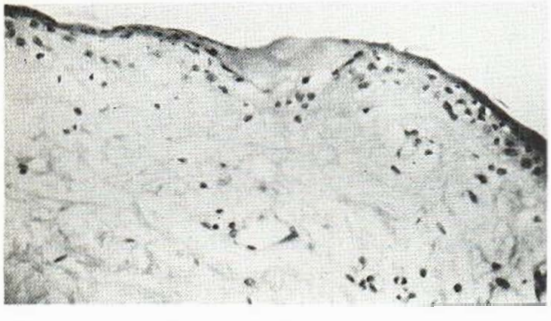

Fig. 5. Atrophy of the skin after 6 weeks' occlusive treatment on normal skin with hydrocortisone 17-butyrate 0.03% in ethanol.

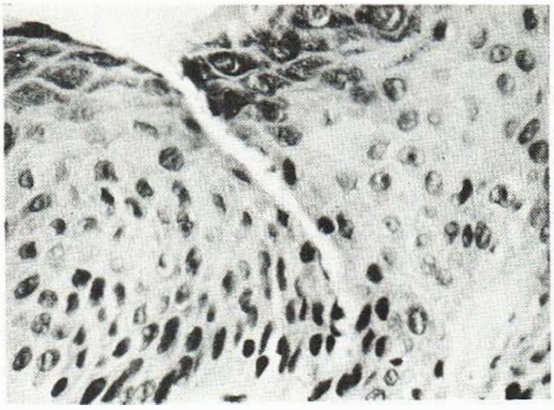

Fig. 6. "Haemorrhagic fissure of the skin" 2 days after finishing 5 weeks' occlusive treatment on normal skin with betamethasone 17-valerate 0.1% cream.

II. *Observations in the different series*

Study 1. 9 out of the 12 volunteers developed erythema craquelé after 6 weeks' application of two potent corticosteroids. There was a correlation between the reactions to Betnovate® cream and to Locoid® cream, such that a reaction to one preparation also gave a reaction to the other.

Studies 2 and 3. The Locoid® cream provoked

Table II. *Data on mean amounts of skin thinning (pre-treatment thickness minus thickness at time of maximum atrophy) associated with different severities of "erythema craquelé" observed following application with different concentrations of hydrocortisone 17-butyrate (HCB) in alcohol/pH 5 and Locoid 0.1% cream*

Treatment	*n*		Absent	Slight/ moderate	Marked
Locoid cream	29		0.61	0.47	0.52
		SD	0.35	0.25	0.38
HCB 0.03%	12		0.59	0.64	0.59
		SD	0.34	0.12	0.31
HCB 0.01%	12		0.54	0.85	0.67
		SD	0.31	0.09	0.18
HCB 0.003%	12		0.54	0.43	[a]
		SD	0.21	0.41	

[a] Only one observation, i.e. "marked" combined with "slight/moderate".

erythema craquelé in 6 of 10 subjects when used during 6 weeks in September–October and in only 1 of 11 subjects when used during 9 days in March–April. No reactions to hydrocortisone cream were observed, nor to the cream base alone or the occlusion alone.

Study 4. Erythema reactions were noticed with all three concentrations: 0.03 %, 0.01 % and 0.003 % hydrocortisone 17-butyrate in alcohol/pH 5 and in one case also to the buffered alcohol solution without corticosteroid. Analysis failed to demonstrate any significant correlation between the strength of the solution and the incidence of erythema craquelé in this small series.

Study 5. All subjects, who had previously reacted with erythema reactions to testing with potent corticosteroids under occlusion, again showed erythema craquelé of varying severity after exposure under occlusion to both the Betnovate® cream and Locoid® cream during 5 weeks in March–April. These creams were at the same time also applied without occlusion. One subject who experienced a very intense erythema craquelé reaction in the occluded sites also had a milder reaction to both creams without occlusion.

III. *Erythema craquelé in relation to skin thinning*

The data on the subjects on whom Locoid® cream was applied were analysed with respect to the mean changes in skin thickness (pre-treatment thickness minus thickness at time for the maximum skin thinning effect) and to the occurrence of erythema craquelé in 12 subjects. No statistical significant correlation was demonstrated between the skin thinning effect and the erythema craquelé (Table II).

DISCUSSION

When *normal* skin on forearms of healthy individuals is exposed long-term to potent corticosteroids under occlusion, a severe skin reaction may be provoked in the test areas after finishing the course of application. The reactions which become visible ½–2 days after finishing the continuous treatment, reach their maximum after about 3 days but occasionally remain visible for up to 6 weeks. Only a few people seem susceptible to provocation of erythema craquelé as demonstrated by this method. In these individuals the response seems to be readily reproducible. They do not appear to get chapping of the skin during wintertime in Sweden any more often than others. It seems that in a few very susceptible individuals the long-term occlusion itself could also predispose to an erythema reaction which is then exaggerated by the corticosteroids. One patient developed a mild erythema craquelé reaction with alcohol/pH 5 without steroid under occlusion. On the other hand, occlusion is not essential in order to produce the reaction, as one subject experienced it after having received two potent commercial steroid preparations for 6 weeks *without* occlusion. At no time during this series was any reaction observed after hydrocortisone therapy. Although there were numerical increases in severity and frequency of erythema reactions with increasing concentrations of hydrocortisone 17-butyrate alcoholic solutions, no statistically significant relationship could be shown in this small series.

The erythema craquelé observed in these studies seems to correspond to the reaction published by Kligman & Frosch (3). They found a correlation between the degree of atrophogenicity of the steroids and the inflammatory reactions. In the present series no correlation could be demonstrated between the intensity of the erythema craquelé and skin thinning measured with the Harpenden caliper technique. There may be a dissociation between a steroid's epidermal effect, causing functional deficiency resulting in erythema craquelé, and the dermal effect responsible for most of the skin thinning seen in the skinfold measurements.

The provocation of erythema craquelé may be of value in "testing" epidermal effects of topical corticosteroids. It is possible that these reactions provoked on normal skin may also be involved in the rebound phenomenon of diseased skin when corticosteroid treatment is stopped.

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