Commercial Glucocorticoid Formulations and Skin Dryness

Could it be Caused by the Vehicle?

HANS CHRISTIAN KORTING, MARTINA KERSCHER, DIETER VIELUF, LUDWIG MEHRINGER, MANFRED MEGELE and OTTO BRAUN-FALCO

Department of Dermatology, Ludwig-Maximilians-Universität, Munich, Federal Republic of Germany

Exzema craquelé can be induced by repeated open application of a topical glucocortocoid, viz. 0.05% clobetasole 17-propionate cream. This might not be invariably due to the active component. Comparison of the skin surface roughness as assessed by profilometry and as expressed by R_{ZDIN} showed a decrease after repeated open application of 0.1% betamethasone 17-valerate cream and 0.25% prednicarbate cream, but an increase following the vehicle of the latter preparation. Thus commercial oil-in-water emulsion preparations seem to be potentially injurious to human skin, though this may be masked when a glucocortocoid is added.

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H. C. Korting, Department of Dermatology, Ludwig-Maximilians-Universität, Frauenlobstr. 9–11, D–8000 München 2, FRG.

As early as in 1979 Kligman & Frosch (1) described a clinical picture encountered after discontinuing prolonged application of topical glucocorticoids, characterized by reddening, tenderness, itch, scratching and scaling. While Kligman & Frosch traced these findings to what they called steroid addiction it has subsequently been described how regular application of topical glucocorticoid preparations can even in a very limited period of time lead to a diseased state presenting as eczema craquelé (erythema craquelé) (2). According to Björnberg (2) this is especially linked to repeated application of potent glucocorticoids in a cream base, such as 0.1% betamethasone 17-valerate or 0.1% hydrocortisone 17-butyrate, when applied under occlusion. Yet in rare cases it may also be due to the open application of a potent steroid cream (over a 6-week period) or to the repeated application of pH 5 ethanol base under occlusion. Eczema craquelé is associated with skin dryness. Skin dryness defined as a clinical condition meaning a rough, finally scaling non-inflamed skin surface can adequately be assessed by using surface profilometry (3). When repeatedly confronted with eczema craquelé as a side effect of the repeated open application of clobetasole 17-propionate cream (0.05%) during a trial performed for the comparative assessment of skin atrophy due to various topical glucocorticoids, we looked for skin surface roughness before and after the application period in a subgroup of 6 healthy volunteers.

MATERIAL AND METHODS

During a double-blind randomized trial, four different formulations were applied to the proximal flexor part of the forearms of 24 healthy volunteers. Application followed a randomized blocks design to ensure that either preparation A or B was applied to the one forearm and preparation C or D to the other. Preparation A representing 0.25% prednicarbate cream, B the corresponding vehicle; C, 0.1% betamethasone 17-valerate cream; C, 0.05% clobetasole

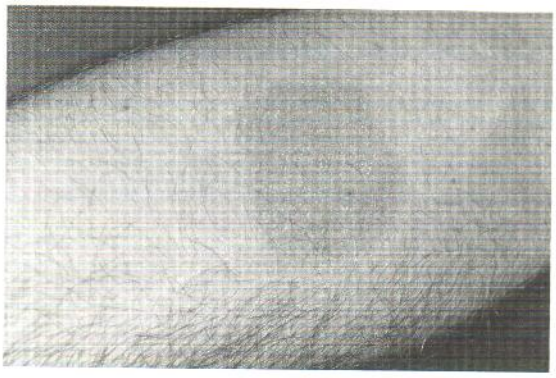

Fig. 1. Eczema craquelé due to the repeated open application of 0.05% clobetasol-17-propionate cream to the proximal flexor part of a healthy human volunteer.

17-propionate cream. Over a 6-week period, about 0.1 g of each preparation was applied to an area measuring 4 × 4 cm both in the morning and in the evening. Further details of the trial, primarily intended to assess skin atrophy, are described elsewhere (4). The sites of application were inspected clinically on days 0, 4, 7, 14, 21, 28, 35, 42 and 63 (i.e. both during and after application). Eczema craquelé was defined by dry, scaly skin with reticulate fissures (5). In 6 volunteers actually representing the last subgroup investigated, profilometry was performed on day 0 and day 42. Replicas of the skin surface were made using a dental silicone rubber impression material (Silasoft N, Detax, Karlsruhe, FRG). Each replica was scanned at six different angles, using the Hommel tester T2000 (Hommel, Villingen-Schwenningen, FRG). Various parameters of roughness as defined by German industrial standards (DIN 4768 and DIN 4762) were determined; for final evaluation, 'mean peak to valley height' (R_{ZDIN}) was chosen (cf. ref. 6). For purposes of comparison, skin thickness data as assessed using high-frequency ultrasound (DUB20, Taberna Pro medicum, Lüneburg, FRG) were available.

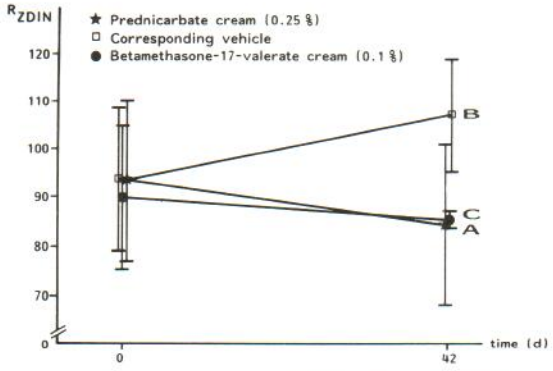

Fig. 2. Mean R_{ZDIN} values representing skin roughness before and after 6 weeks' application of 0.25% prednicarbate cream (*A*), the corresponding vehicle (*B*) and 0.1% betamethasone-17-valerate cream (*C*).

RESULTS

In 8 out of 12 volunteers applying 0.05% clobetasol 17-propionate cream, clear-cut eczema craquelé was found, making immediate discontinuation of treatment inevitable for safety reasons. Once only treatment had to be stopped after 14 days; 7 times after 21 days. Fig. 1 shows the typical clinical picture of eczema craquelé caused by 0.05% clobetasole 17-propionate cream. The ages of the volunteers showing this side effect ranged from 24 to 29 years, the ages of the others from 24 to 32 years. Five volunteers showing manifest eczema were female, while 2 were female in the other subgroup.

Of the 6 volunteers in whom skin roughness was assessed, 3 received 0.25 prednicarbate cream, 3 the corresponding vehicle, 4 0.1% betamethasone 17-valerate cream, and 2 0.05% clobetasole 17–propionate. Both volunteers applying the latter preparation had to discontinue treatment earlier than planned due to eczema craquelé. Hence data representing the treatment effect after 6 weeks are not available for this subgroup. While R_{ZDIN} values tended to decrease with preparation A as well as C, they tended to increase with preparation B (Fig. 2).

DISCUSSION

Eczema (or erythema) craquelé following the repeated open (or closed) application of glucocorticoid creams to normal human skin has been interpreted as an unwanted effect of the active ingredient (2). In one case, however, identical findings have been linked to the (closed) application of ethanol pH 5 (21). Moreover it has been stated that even widely accepted commercial moisturizers might act as irritants (7). The present findings first substantiate the idea that eczema craquelé can be a frequent sequela of the repeated open application of a potent glucocorticoid cream. This can be deduced from the frequency of *Etat craquelé* during the use of 0.05% clobetasol 17-propionate cream. This effect, however, need not be linked to the glucocorticoid itself. This can be concluded from the findings with 0.25% prednicarbate cream and the corresponding vehicle. It was in fact the vehicle which was irritant in this case, while the corresponding glucocorticoid preparation was not. Hence, prednicarbate seems to be able to over-compensate the unwanted effect of the cream base chosen by its manufacturer. This in a way seems to contradict a recent finding by Van der

Valk & Maibach (8) that several topical glucocorticoids are not able to suppress irritant skin reaction elicited by sodium laurylsulfate solution. As commercial glucocorticoid cream bases can be assumed to be free of components with well-known irritancy potential, one might be tempted to speculate that it is simply the comparatively high water content of the oil-in-water emulsion which reduces the water-binding capacity and thus gives way to desiccation. This question must be subjected to further analysis. The area of application of the drug chosen here might in fact represent the optimum area for pertinent analysis, as the potential irritation has been shown to increase from the wrist to the cubital fossa (9).

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