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Topical Glucocorticoids of the Non-fluorinated Double-ester Type

Lack of Atrophogenicity in Normal Skin as Assessed by High-frequency Ultrasound

M. J. KERSCHER and H. C. KORTING

Department of Dermatology, Ludwig-Maximilians-Universität, München, Germany

With the advent of non-fluorinated double esters the spectrum of topical dermatotherapy with glucocorticoids seems to have broadened to include safer congeners. To assess the atrophogenicity potential of glucocorticoids, high-frequency ultrasound has been proposed. In a comparative trial using the DUB 20 system, 24 healthy volunteers applied hydrocortisone aceponate, the corresponding vehicle, prednicarbate ointment and betamethasone-17-valerate ointment over a period of 6 weeks. While both hydrocortisone aceponate and prednicarbate ointment induced no significant reduction in skin thickness, the onset of epidermal – dermal thinning with betamethasone-17-valerate was early and the extent marked. These findings imply an increased therapeutic index with the non-fluorinated double esters. ***Key words: Hydyocortisone aceponate; Atrophogenicity; High-frequency ultrasound.***

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M. J. Kerscher, Department of Dermatology, Ludwig-Maximilians-Universität München, Germany.

Topically applied glucocorticoids constitute a major breakthrough in dermatotherapy (1). Clinical experience with conventional fluorinated topical glucocorticoids, however, indicated that a high anti-inflammatory activity was paralleled by a high skin atrophy potential (2, 3). Thus, topical glucocorticoids highly effective against inflammation yet showing a reduced skin thinning potential would be desirable therapeutic agents. Since the recognition of this problem there have been many attempts to produce topical glucocorticoid preparations showing a dissociation of the wanted anti-inflammatory activity from the unwanted antiproliferative effect. The list of such substances ranges from still halogenated ones such as mometasone furoate to non-fluorinated double esters. Esterification has proved to be a particularly effective method for increasing the pharmacological activity of topical glucocorticoids (4). Hydrocortisone-21-acetate-17-propionate, for short hydrocortisone aceponate, belongs to this type of steroidal drug. The effect of hydrocortisone aceponate on proliferation, total protein and collagen synthesis of human skin fibroblasts has already been assessed in vitro. When compared with betamethasone-17-valerate and clobetasol-17-propionate, hydrocortisone aceponate inhibits the incorporation of [^{3}H]-thymidine in DNA in human skin fibroblasts less than the halogenated glucocorticoids betamethasone-17-valerate and clobetasol-17-propionate (5). According to this study, prednicarbate, another non-fluorinated double ester already introduced in 1986, ranks between hydrocortisone aceponate and the halogenated glucocorticoids.

In addition to these in vitro tests, the use of high-frequency ultrasound is considered to be a suitable non-invasive in vivo method with low risk, high reliability, validity and reproducibility for the determination of the atrophogenicity potential of topically applied glucocoriticoids (6, 7). To evaluate further the atrophogenicity potential of these glucocorticoids in vivo, we have performed a double-blind, controlled trial comparing hydrocortisone aceponate, prednicarbate, the vehicle of hydrocortisone aceponate and betamethasone-17-valerate using high-frequency ultrasound with A- and B-scans.

MATERIALS AND METHODS

In a double-blind controlled trial based on a design approved by the local medical ethics committee and complying with the requirements of the Helsinki Declaration, 24 healthy adult volunteers (11 males, 13 females, age range 22–57 years, mean age 31.8 ± 10.8 years) with no history of skin disease applied two out of a total of four different preparations to the volar part of their forearms.

The four different treatment modalities were:
hydrocortisone aceponate ointment (A),
vehicle of hydrocortisone aceponate ointment (B), prednicarbate ointment (C),
betamethasone-17-valerate ointment (D).

Allocation of the treatment modalities to the left or right forearm followed a partially balanced incomplete block design. Both in the morning and in the evening, about 0.1 g of the test preparation was applied to an area of 4 × 4 cm on the flexor part of the forearm close to the elbow. The test area was not to be covered within the next 10 min following application and not to be cleansed during the 2 h to follow. The entire application period spanned 6 weeks. Both test areas were inspected on days −2, −1, 0, 4, 7, 14, 21, 28, 35, 42 (end of treatment) and on day 63 (3 weeks after the end of treatment period). Analysis included both visual assessment of skin thinning as well as other potential side effects such as teleangiectasia and dryness (exsiccation). Moreover, skin thickness was assessed using 20 MHz ultrasound.

To assess skin thickness, A- and B-mode images were used. This was made possible by using the DUB 20 system (Tpm, Lüneburg, Germany) described earlier (8). At each point in time, two different B-mode images within the test area and one B-mode image outside (untreated control area) were taken and stored on floppy discs. Each B-mode image taken was used to select five different spots where A-mode images were analysed for skin thickness, being defined as thickness of both epidermis and corium.

For the statistical analysis, mean values and standard deviation were calculated. Furthermore an analysis of variance for the incomplete randomized block design was used. Parallelized comparisons of the treatment modalities were carried out using the error variance of the analysis of variance. Multiple testing of the treatments to be compared were done following the procedure of Bonferroni-Holm.

The change in skin thickness (thickness of epidermis and corium) after 42 days of treatment with the four different treatment modalities was the main parameter of the confirmatory analysis. $p < 0.05$ was to be considered significant.

Table I. *Mean values of skin thickness after 6 weeks' application of the four treatment modalities.*

Day	Skin thickness: x + SD [μm]			
	Hydrocortisone aceponate	Corresponding base	Prednicarbate	Betamethasone-17-valerate
0	1189±149	1201±106	1209±127	1193±122
42	1038±134	1091±125	1072±106	979± 96

RESULTS

While skin thickness was about equal at the sites of investigation before treatment, some differences were evident after 6 weeks' treatment according to the four different treatment modalities (Table I). The development of skin thickness relative to the initial value under the different treatment modalities is shown in Fig. 1. Over the entire course of the study, none of the volunteers showed visual signs of cutaneous atrophy, i.e. teleangiectasia, shininess, striae distensae, bruising, loss of elasticity and loss of normal skin markings. Furthermore, no other treatment-related adverse experiences were reported by any of the 24 volunteers enrolled in this study.

After treatment with both hydrocortisone aceponate ointment and prednicarbate ointment for 42 days, there were no statistically significant differences in skin thickness when compared with the baseline. Furthermore, application of the vehicle of hydrocortisone aceponate produced no significant change in skin thickness. Although the reduction in skin thickness was slightly greater with prednicarbate ointment than with hydrocortisone aceponate ointment and the corresponding vehicle of the latter ointment, these differneces were not significant. With betamethasone-17-valerate ointment, however, a statistically significant difference in skin thickness could be demonstrated.

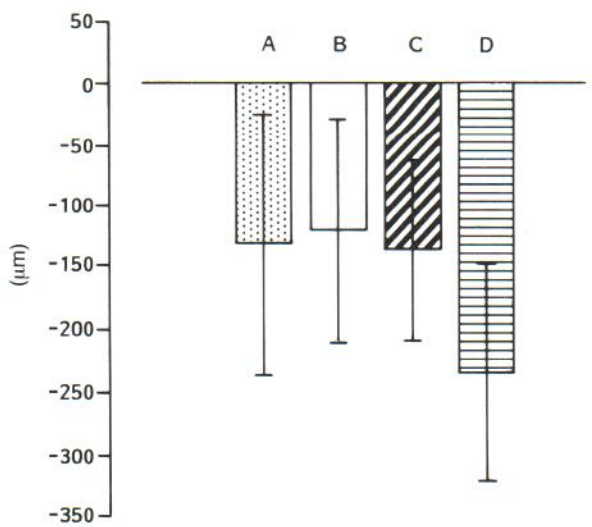

Fig. 1. Development of skin thickness (mean value ± standard deviation) relative to the initial value under the different treatment modalities. *A*, Hydrocortisone aceponate ointment; *B*, vehicle of hydrocortisone aceponate ointment; *C*, prednicarbate ointment; *D*, betamethasone-17-valerate ointment.

DISCUSSION

Cutaneous atrophy and its associated manifestations, i.e. teleangiectasia, striae, shining, belong to the most serious and readily visible local side effects of topical corticosteroid therapy. The attempts to modify the glucocorticoid molecule to separate the wanted antiinflammatory potency from the unwanted atrophogenicity potential has been a major research goal in the field of dermatotherapy (3). One result of such efforts has been the development of non-fluorinated double esters such as hydrocortisone aceponate and prednicarbate. This study was designed to test the atrophogenicity potential of these newly developed glucocorticoids in comparison with that of betamethasone-17-valerate.

According to the present findings, fluorinated, non-esterified topical glucocorticoids such as betamethasone-17-valerate, markedly reduce the thickness of normal human skin when applied openly twice daily over a period of 6 weeks, while this is not the case with the newer non-fluorinated double esters hydrocortisone aceponate and prednicarbate, provided that these glucocorticoids are used in conventional concentrations and preparations respectively. It is noteworthy that even after 6 weeks of treatment twice daily with either of the two double esters, no signs of cutaneous atrophy could be observed. As shown in a previous study, with most of the conventional glucocorticoids the development of cutaneous atrophy usually becomes detectable after treatment periods as short as 3 weeks (9). Our results obtained by using a sensitive technique with high reliability, validity and reproducibility – even capable of detecting subtle or covert signs of cutaneous atrophy as shown in the case of betamethasone-17-valerate – demonstrate no atrophogenic potential of hydrocortisone aceponate or prednicarbate. The results confirm previous findings with prednicarbate (9, 10). Moreover, the findings with hydrocortisone aceponate imply that the low atrophogenicity potential of the former glucocorticoid is not a unique feature, but a feature common to the new class of non-fluorinated double esters. As shown by Vogt & Höhler, the clinical efficacy of prednicarbate 0.25% is equivalent to betamethasone-17-valerate 0.1% in appropriate vehicles (11). Furthermore, Flasch & Klaschka have demonstrated a comparable efficacy of hydrocortisone aceponate and betamethasone-17-valerate in appropriate vehicles, at least in atopic eczema (12). These findings, taken together, imply an increased therapeutic index with the non-fluorinated double esters.

This hypothesis is to be substantiated further by an ongoing trial of hydrocortisone-17-butyrate-21-acetate, another congener. As yet the clinical relevance of such findings in patients

suffering from inflammatory skin diseases deserves future interest.

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