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Clobetasol-17-propionate lotion under hydrocolloid dressing (Duoderm ET) once weekly versus unoccluded clobetasol-17-propionate ointment twice daily in psoriasis: an immunohistochemical study on remission and relapse

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Abstract **It is well established that the efficacy of corticosteroids under occlusion with hydrocolloids (HCD) is superior compared to monotherapy with topical corticosteroids. However, following treatment with more potent corticosteroids, increased side effects and a more pronounced rebound might be expected. In the present clinical study, the efficacy of relapse after and the safety characteristics of two treatment modalities were compared: clobetasol-17-propionate lotion under an HCD dressing once weekly versus clobetasol-17-propionate ointment without an HCD twice daily. Clinical assessments were recorded and skin biopsies were taken before therapy, at clearance and 6 weeks after clearance. A panel of monoclonal antibodies to characterize epidermal proliferation, differentiation and inflammation were selected. In addition, clinical and histological assessments for skin atrophy were made. Both therapies had a major therapeutic effect, which was reflected in the clinical and immunohistochemical parameters. The only difference between the two therapies was a faster remission induction time in patients treated with corticosteroids combined with HCD. Six weeks after discontinuation of treatment, similar clinical and histological signs of relapse were observed for both therapies. Clinically, there were no signs of skin atrophy but histologically, epidermal thinning occurred to the same extent with both therapies but proved to be reversible within 6 weeks of discontinuation of treatment. From this study it can be concluded that the combination of HCD and corticosteroids is able to induce relatively fast remission compared to corticosteroid monotherapy but relapse and safety characteristics are comparable to the unoccluded corticosteroid therapy.**

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Introduction

Topical corticosteroids have been widely utilized in steroid-responsive dermatoses such as psoriasis, and their efficacy and safety have been studied extensively. Low- and medium-potency corticosteroids are used for maintenance therapy in mild and moderate disease. Rapid remissions in more severely affected skin can be obtained using potent corticosteroids[4]. Adverse events from the use of topical corticosteroids can be divided into local and systemic effects. Local adverse events such as skin thinning are frequently observed. Systemic adverse events such as suppression of the adrenal cortex are more serious [4, 9, 10].

Different therapeutic schedules and modes of application have been used in corticosteroid therapy. During the last decade treatment with corticosteroids under occlusive dressings has become a popular approach. Hydrocolloid dressings (HCD), used for occlusive therapy, are convenient to wear and have a beneficial effect on psoriatic plaques even as monotherapy without corticosteroids [5,6]. In vivo studies show that monotherapy of psoriatic plaques with occlusive dressings decreases the number of cell layers positive for involucrin and transglutaminase (TGase) [3], whereas the mitotic activity, keratin 16 expression and dermal T cell accumulation tend to decrease [14]. It has been established that the efficacy of corticosteroids combined with HCD is superior compared to corticosteroids without HCD occlusion, but information on relapse and safety is sparse [2,7,15].

Recently, a study was carried out of clinical efficacy, immunohistochemical response and safety of once-weekly applications of clobetasol-17-propionate (clobetasol) [9] lotion under occlusion with the HCD Duoderm ET in comparison with clobetasol ointment applied twice daily without occlusion. The study was part of a larger multicentre study [16]. Skin biopsies for immunohistochemistry were taken before treatment, at clearance and 6

Table 1 Monoclonal antibodies used in the present study

Antigen	Antibody	Source	Dilution	Staining technique
Ki-67	MIB-1	Immunotech, France	1:50	Indirect immunoperoxidase
Involucrin	Mon-150 [1]	Dr. J van Duijnhoven, Holland	1:25	Indirect immunoperoxidase
Transglutaminase	BT621	Biomedical Technologies, USA	1:100	Indirect immunoperoxidase
Filaggrin	BT576	Biomedical Technologies, USA	1:500	Indirect immunoperoxidase
CD2	DAKO-T11	Dakopatts, Denmark	1:100	Avidin-biotin complex method
Elastase	DAKO-elastase	Dakopatts, Denmark	1:100	Indirect immunoperoxidase

weeks after discontinuation of treatment. Immunohistochemical markers for epidermal proliferation, differentiation and inflammation were assessed (Table 1). The remission, relapse and safety characteristics of the two treatments were also compared. In particular, the following questions were addressed: (1) what are the differences in immunohistochemical response between treatment with a potent topical corticosteroid under HCD and treatment with the corticoid without HCD in chronic plaque psoriasis, and (2) what are the differences with respect to remission, relapse and safety characteristics between the two therapies.

Materials and methods

Study design

A group of 19 patients with chronic plaque psoriasis was included in an open, comparative study. One lesion on each patient up to 70 cm^2 in area was treated with either clobetasol lotion (Dermovate Lotion; Glaxo, Zeist, The Netherlands) under occlusion with HCD (Duoderm ET; Convatec, Woerden, The Netherlands) with a change of dressing and lotion once weekly (ten patients), or clobetasol ointment (Dermovate ointment; Glaxo) applied twice daily (nine patients).

The patients were treated for a maximum of 6 weeks or until clearance of the lesion. Clinical assessments were carried out every 2 weeks. After clearance, no therapy was allowed and the patients visited the department every 2 weeks until the first signs of relapse of the psoriatic lesion were observed. The final investigation was 3 weeks after the first sign of relapse.

In all patients 3-mm punch biopsies were taken from the target lesions before treatment, and immediately after and 6 weeks after discontinuation of treatment. The biopsy procedure has been described before [11, 13].

Patients

The group of 19 patients consisted of 16 males and 3 females, with ages ranging from 32 to 79 years. Apart from the psoriasis, the patients did not have other significant dermatological or internal diseases. No treatment for psoriasis was allowed other than the trial medication. Concomitant treatments, which did not interfere with psoriasis or test medications, were permitted to continue. Before study initiation, no topical antipsoriatic treatment had been administered for 2 weeks and the patients had not used systemic treatment for at least 6 weeks. Permission of the local Ethics Committee and written informed consent were obtained from all patients.

Assessment of clinical efficacy

Clinical efficacy was assessed using the sum-score of the three clinical severity parameters erythema, induration and scaling, each of them scored on a 0–4 point-scale (0, no involvement; 1, mild involvement; 2, moderate involvement; 3, marked involvement; 4, severe involvement). Photographs were taken at each visit. Remission was defined as no or only a mild erythema without induration or scaling (sum-score ≤ 1). Relapse was defined as any increase in the sum-score. The length of the remission period and the sum-score at the time of relapse were also recorded.

Immunohistochemical stainings

For the immunohistochemical stainings a panel of monoclonal antibodies (Table 1) were used. All antibodies were diluted in phosphate buffered saline (PBS). This immunoperoxidase technique was as described previously [11, 13]. Staining with DAKO-T11 was done by the avidin-biotin complex method (ABC kit (mouse), Vector Laboratories, Burlingame, Calif.). In brief, the slides were incubated with 20% normal horse serum and subsequently with the T11 antibody for 60 min. The slides were incubated with horse anti-mouse biotinylated IgG (1:200, Vector Laboratories) for 30 min. After two washes with PBS a 30-min incubation with avidin-biotin-peroxidase complex (1:50, Vector Laboratories) was performed. Visualization was done using a solution of 3-amino-9-ethylcarbazole (AEC). All slides were counterstained with Mayer's haematoxylin (Sigma, St Louis, Mo.) and mounted in glycerol/gelatine.

Histological examination

The histological examination was performed blinded. The scoring methods used have been used and reported previously [11, 13]. Epidermal proliferation was measured by counting the number of Ki-67 positive nuclei per millimetre length of section. Involucrin and TGase expression were assessed by calculation of the ratio of-positive cell layers to total cell layers of the viable epidermis. This was done at two sites: above the dermal papilla and between the dermal papillae. In addition, the total number of cell layers was recorded. Filaggrin expression was assessed by determining the percentage of the length of the stratum corneum and stratum granulosum that was stained. Inflammation (PMN and T lymphocytes) was assessed separately for the dermis and the epidermis. Dermal inflammation was evaluated semiquantitatively by expressing the number of positively stained cells as a percentage of the total number of infiltrate cells: 0, no positive cells; 1, sporadic; 2, 1–25%; 3, 26–50%; 4, 51–75%; 5, 76–99%; 6, 100%. Epidermal inflammation was assessed using a 0–4 point scale: 0, no staining; 1, sporadic staining; 2, minimal staining; 3, moderate staining; 4, pronounced staining.

Assessment of skin atrophy

During the study clinical signs of atrophy were recorded. Histological atrophy was recorded in terms of counting the total number of cell layers of the epidermis between the dermal papillae.

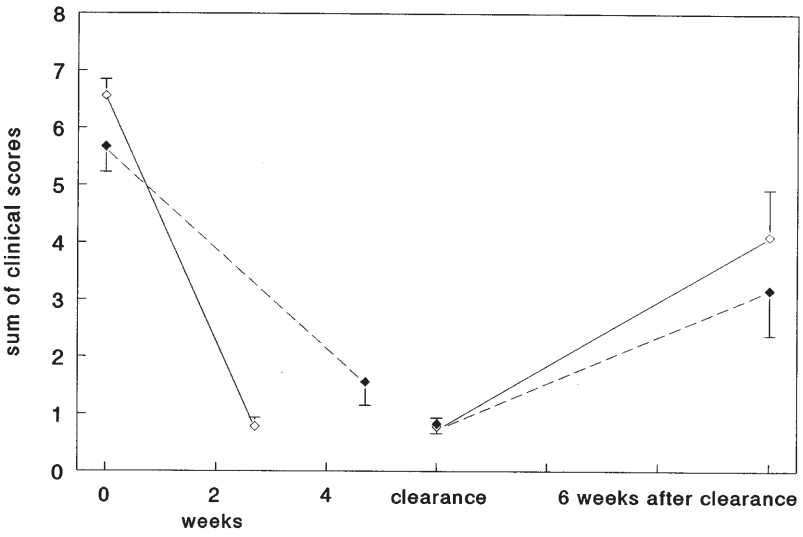

Fig. 1 The course of the sum of the clinical scores (erythema, induration and scaling) during treatment and after discontinuation of treatment with clobetasol lotion under occlusion with hydrocolloid (——) or monotherapy with clobetasol ointment (– – –)

Table 2 Sum-scores and individual scores for erythema, induration and scaling, before clobetasol treatment, at clearance, and 6 weeks after clearance (means)

Clinical sign	Before treatment		Clearance		6 weeks after clearance	
	Lotion + HCD	Ointment	Lotion + HCD	Ointment	Lotion + HCD	Ointment
Erythema	2.20	1.67	0.78	0.89	1.33	1.00
Induration	1.90	1.67	0.00	0.33	1.33	0.83
Scaling	2.60	2.33	0.00	0.33	1.44	1.33
Sum	6.70	5.67	0.78	1.56	4.11	3.17

Table 3 Immunohistochemical scores before clobetasol treatment, at clearance, and 6 weeks after clearance (means ± SEM)

Antigen	Localization	Before treatment		Clearance		6 weeks after clearance	
		Lotion + HCD	Ointment	Lotion + HCD	Ointment	lotion + HCD	Ointment
Ki-67	Basal layer	209 ± 27	243 ± 40	43 ± 28	39 ± 22	127 ± 27	141 ± 26
Involucrin	Interpapillar	0.59 ± 0.05	0.53 ± 0.03	0.41 ± 0.04	0.40 ± 0.04	0.52 ± 0.05	0.50 ± 0.02
	Above papilla	0.76 ± 0.06	0.89 ± 0.04	0.61 ± 0.03	0.66 ± 0.05	0.81 ± 0.03	0.81 ± 0.03
TGase	Interpapillar	0.56 ± 0.03	0.63 ± 0.03	0.38 ± 0.03	0.41 ± 0.04	0.55 ± 0.05	0.56 ± 0.04
	Above papilla	0.87 ± 0.02	0.90 ± 0.02	0.58 ± 0.04	0.60 ± 0.06	0.79 ± 0.04	0.78 ± 0.05
Filaggrin	Granular layer	69 ± 7.3	65 ± 8.7	97 ± 1.5	94 ± 3.3	71 ± 10	82 ± 10
	Corneal layer	44 ± 9.0	47 ± 12	97 ± 2.4	100 ± 0	64 ± 13	76 ± 13
CD2	Dermis	4.8 ± 0.32	4.9 ± 0.4	2.4 ± 0.24	2.8 ± 0.5	4.1 ± 0.4	3.8 ± 0.7
	Epidermis	3.3 ± 0.3	2.9 ± 0.4	0.56 ± 0.17	0.50 ± 0.34	2.7 ± 0.4	2.2 ± 0.6
Elastase	Dermis	1.0 ± 0.4	1.1 ± 0.4	0.22 ± 0.15	0 ± 0	1.0 ± 0.4	0.67 ± 0.3
	Epidermis	1.4 ± 0.4	2.2 ± 0.4	0 ± 0	0 ± 0	2.2 ± 0.5	1.2 ± 0.6

Statistical evaluation

Data are reported as means ± SEM. Changes in paired markers, due to therapy, were evaluated using the *t*-test for paired values. Unpaired data were analysed using a *t*-test assuming equal variances. A two-tailed hypothesis was employed to interpret data. A *P*-value ≤ 0.05 was regarded as statistically significant.

Results

Clinical response

Of the 19 patients who participated in the study, 15 achieved clearance and completed the study. One patient, treated with clobetasol lotion and HCD, was excluded from the study because of impetiginization during treatment. Three patients who were treated with clobetasol ointment did not achieve clearance after 6 weeks and therefore did not participate in the follow-up period. The mean treatment time in the lotion + HCD group was 2.7 ± 0.3 weeks which was significantly shorter than in the ointment group (4.7 ± 0.7 weeks; mean ± SEM; $P = 0.02$). The length of the remission was equal for both therapies (clobetasol lotion + HCD 5.3 ± 1.1 weeks, and clobetasol ointment 5.3 ± 1.0 weeks; mean ± SEM). The severity of the relapse was also similar following both treatments.

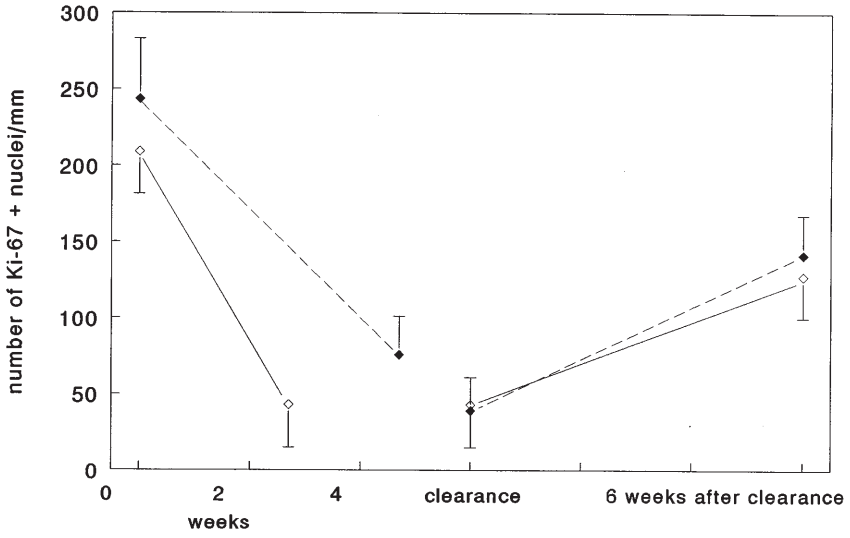

Fig. 2 The number of Ki-67-positive nuclei per millimetre of the epidermis during treatment and after discontinuation of treatment with clobetasol lotion under occlusion with hydrocolloid (——) or monotherapy with clobetasol ointment (– – –)

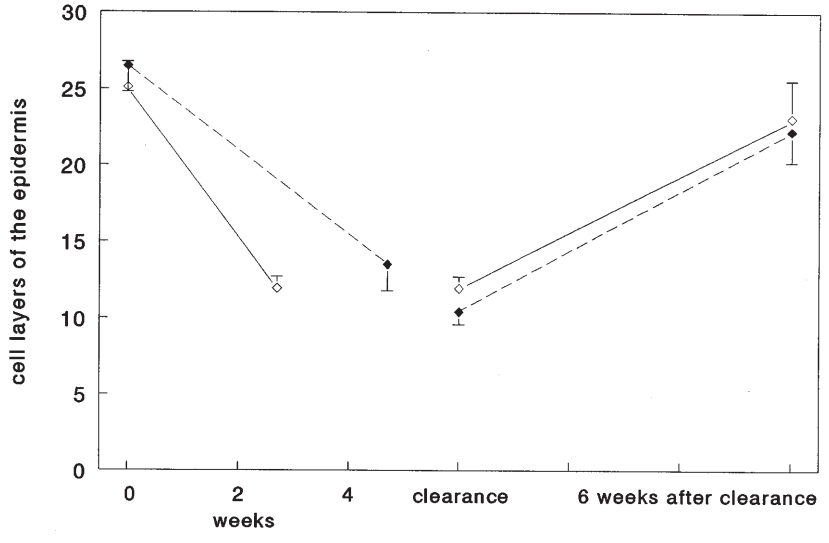

Fig. 3 The number of cell layers of the epidermis during treatment and after discontinuation of treatment with clobetasol lotion under occlusion with hydrocolloid (——) or monotherapy with clobetasol ointment (– – –)

The results of the clinical assessments, indicated by the sum-score, are shown in Fig. 1. Individual scores for erythema, induration and scaling are shown in Table 2. During both treatments a statistically significant decrease in the sum-score was observed (clobetasol lotion + HCD, $P < 0.001$; clobetasol ointment, $P < 0.001$). The scores in the two treatment groups at the start of therapy did not differ significantly, neither did the scores at the end of the treatment period. Clearing was reached in 15 patients (clobetasol lotion + HCD, 9 patients; clobetasol ointment; 6 patients). Six weeks after discontinuation of treatment, 13 patients had experienced a relapse with a substantial increase in the sum-scores (clobetasol lotion + HCD, $P = 0.002$; clobetasol ointment, $P = 0.08$). There was no significant difference between the two therapies with respect to the sum-scores 6 weeks after discontinuation of treatment. The sum-score at the end of the 6 weeks posttreatment follow-up was significantly lower than the sum-score at the start of the study (clobetasol lotion + HCD, $P = 0.02$; clobetasol ointment; $P = 0.01$).

Immunohistochemical assessments

With respect to all immunohistochemical stainings, both therapies induced significant changes during treatment ($P \leq 0.05$; Table 3). Both at the start of therapy and at clearance there was no significant difference between the two treatment groups. In Fig. 2, the response to both therapies is illustrated by the number of Ki-67-positive nuclei in the epidermis.

Six weeks following discontinuation of both treatments, all immunohistochemical markers had changed substantially (Table 3) and these changes, indicating a relapse in psoriasis, were comparable between the two treatment groups (Table 3). Six weeks after clearance, there was a significant decrease in the Ki-67 count ($P = 0.05$) and a significant decrease in the CD2-positive cells in the epidermis ($P = 0.05$) for the patients treated with clobetasol lotion + HCD group compared with the pretreatment values and a significant decrease in TGase above the papilla in the patients treated with clobetasol ointment ($P = 0.02$). The other parameters showed no statistically significant changes.

Assessment of epidermal atrophy

No clinical signs of atrophy were seen. The results of the counting of the number of cell layers are shown in Fig. 3. Both treatments led to a significant decrease in the number of cell layers (clobetasol lotion + HCD, $P < 0.001$; clobetasol ointment, $P < 0.001$), but there was no difference between the two therapies. After discontinuation of the two therapies a similar and significant increase in the number of cell layers was observed (clobetasol lotion + HCD, $P = 0.004$; clobetasol ointment, $P = 0.05$). For both therapies, at the end of the 6 week follow-up, the number of cell layers was not significantly different compared to the situation at the start of therapy.

Discussion

The clinical results of the present study are in line with those of the multicentre comparative study [16], and show a faster induction of remission in the clobetasol lotion + HCD group compared with the clobetasol ointment group and equal clinical relapse characteristics in the two treatment groups.

In the present study, significant changes occurred during treatment in all immunohistochemical markers analysed (Table 3). The degree of immunohistochemical changes did not differ significantly between the two therapies. Despite clinical clearance, only some of the immunohistochemical markers reached the values of normal human skin [12]. Filaggrin, TGase and elastase stainings reached the normal range in both treatment groups.

Following discontinuation of corticosteroid treatment, for both treatments, clear signs of relapse of psoriasis were seen after 6 weeks or less. This might limit the treatment of psoriasis. The immunohistochemical markers also changed substantially (Table 3). Comparison of the two therapies for the immunohistochemical markers 6 weeks after clearance, did not reveal any significant differences. This observation confirms and strengthens the conclusion of the clinical data of the multicentre study [16] that both treatments have a similar posttreatment response pattern.

Clinically, signs of skin atrophy were not observed in any of the patients. Histologically, the number of epidermal cell layers demonstrated a significant decrease during therapy. Persisting local side effects such as striae and skin thinning after topical corticosteroid treatment are mainly the result of dermal atrophy, but epidermal thinning may also give insight into atrophogenecity [8]. The epidermal thinning observed in the present study proved to be reversible after discontinuation of both treatments within the 6-week posttreatment observation period. Some authors suggest that corticosteroids under occlusion should be regarded as potentially more atrophogenic than corticosteroids without occlusion and should therefore be avoided [10]. The present study, however, indicates that the combination of clobetasol and HCD does not differ from monotherapy with clobetasol in inducing epidermal atrophy.

In conclusion, the present study demonstrates a similar immunohistochemical response of the combination of clobetasol lotion under HCD compared with monotherapy with clobetasol ointment. No immunohistochemical indication for a faster relapse following discontinuation of clobetasol lotion in combination with HCD compared with monotherapy with clobetasol ointment was seen. With respect to the thickness of the epidermis the combined approach was not more atrophogenic than monotherapy. In addition, clobetasol lotion applied once weekly under HCD induced a faster clearing compared to clobetasol ointment twice daily. Therefore treatment with clobetasol lotion under HCD reduces the duration of treatment as well as the quantity of topical corticosteroid required to achieve clearing.

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