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Calcipotriol cream with or without concurrent topical corticosteroid in psoriasis: tolerability and efficacy

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Summary The objectives of the study were to determine whether concurrent treatment with calcipotriol (50 μg/g) and either clobetasone 17-butyrate cream (0·5 mg/g) (moderate potency) or betamethasone 17-valerate cream (1 mg/g) (potent) or placebo (vehicle of calcipotriol) was more effective and/or caused less skin irritation than calcipotriol cream (50 μg/g) used twice daily. It was a multicentre, double-blind, parallel group study. Patients applied calcipotriol cream in the morning and either vehicle ($n = 174$), calcipotriol ($n = 174$), clobetasone ($n = 175$) or betamethasone creams ($n = 176$) in the evening for up to 8 weeks. Adverse events led to withdrawal in 20 patients (2·9%). The mean percentage change in PASI (psoriasis area and severity index) was −40·6 in the calcipotriol/vehicle group, −48·3 in the calcipotriol/calcipotriol group, −53·7 in the calcipotriol/clobetasone 17-butyrate group and −57·5 in the calcipotriol/betamethasone 17-valerate group. A statistically significant difference was seen between the four treatment groups ($P = 0·006$) with calcipotriol/vehicle being less effective than the other treatments. A statistically significant difference in favour of calcipotriol/betamethasone 17-valerate was seen between the calcipotriol/calcipotriol group and the calcipotriol/betamethasone 17-valerate group. The majority of adverse events were skin irritations, which were reported for 31·2% of patients treated with calcipotriol/vehicle, 34·3% of patients treated with calcipotriol twice daily and 23·8% vs. 17·1% of patients treated with calcipotriol/clobetasone 17-butyrate and calcipotriol/betamethasone 17-valerate, respectively. Skin irritation was seen statistically significantly less frequently in patients treated with calcipotriol/clobetasone 17-butyrate or calcipotriol/betamethasone 17-valerate ($P = 0·001$), whereas no difference was seen between the other groups. In conclusion, calcipotriol applied twice daily was as effective as calcipotriol/clobetasone 17-butyrate, but slightly less effective than calcipotriol/betamethasone 17-valerate. The incidence of skin irritation was less for patients using concurrent corticosteroids, whereas treatment with calcipotriol/vehicle did not reduce the incidence of skin irritation when compared with calcipotriol twice daily.

Treatment with calcipotriol ointment (50 μg/g) or calcipotriol cream (50 μg/g) applied twice daily is considered to be effective in about two out of three patients, but complete clearance of psoriasis is not commonly reported. Furthermore, twice-daily application of calcipotriol ointment may result in skin irritation in 5–25% of the patients.[1–5] A similar proportion of patients experiences skin irritation using calcipotriol (50 μg/g) twice daily in a cream formulation.[6,7] Although the skin irritation is often mild, it may impair compliance and eventually result in premature termination of the treatment.

The purpose of the present study was therefore to identify the efficacy and safety of alternative treatment regimens to twice-daily application of calcipotriol. Once-daily application of calcipotriol alone might suffice to decrease the irritation by calcipotriol and still provide acceptable efficacy. Alternatively, the concurrent use of

calcipotriol and a topical corticosteroid, both used once daily, might negate the irritation induced by calcipotriol. Additionally, the concurrent use of calcipotriol and a corticosteroid might improve the therapeutic efficacy compared with calcipotriol alone.

This study, therefore. explored the concurrent use of topical calcipotriol and either a moderate-potency (clobetasone 17-boutyrate 0·5%) or a potent (betamethasone 17-valerate 0.l%) corticosteroid compared with once-daily and twice-daily applications of calcipotriol cream alone in an attempt to identify treatment regimens that could increase the number of patients who would benefit from calcipotriol therapy.

Materials and methods

Study design

The study was a multicentre (53 centres in six countries), randomized, double-blind, controlled comparison of the following four treatments: (i) calcipotriol cream (50 μg/g) (morning) and vehicle cream (evening); (ii) calcipotriol cream (50 μg/g) applied twice daily (morning and evening); (iii) calcipotriol cream (50 μg/g) (morning) and clobetasone 17-butyrate cream (0·5 mg/g) (evening); (iv) calcipotriol cream (50 μg/g) (morning) and concurrent betamethasone 17-valerate cream (1 mg/g) (evening).

The study consisted of two phases: a wash-out/qualification phase of 2 weeks, during which patients used only a non-medicated emollient; and a randomized, double-blind treatment phase lasting 8 weeks, during which patients were seen after 2, 4 and 8 weeks. The maximum dose allowed was 120 g/week. Trial medication was not applied on the scalp and face. In these areas, patients were allowed to use tar/dithranol preparations or low- to medium-potency corticosteroids.

Patients

Subjects were of either sex, aged 18 years and above with psoriasis vulgaris on the trunk and/or limbs. Women of child-bearing age were required to have a negative pregnancy test at study entry and to use an adequate method of contraception for the duration of the study. Patients with markedly deteriorating or spontaneously improving psoriasis during the wash-out phase, patients who had used systemic anti-psoriatic treatment, PUVA or UVB within 6 weeks before study entry, patients treated with any other medication (systemic or topical) that could affect the course of the disease, patients with hypercalcaemia, significant renal disease or who intended to spend time in a sunny climate during the study period were excluded. Women who were pregnant, wished to become pregnant or were breastfeeding were also excluded.

Assessment of efficacy

Investigator's clinical assessment. At each visit, the investigator assessed the extent of the patient's psoriasis and the severity of redness, thickness and scaliness. Based on these scores, the psoriasis area and severity index (PASI) was calculated.[3] At weeks 2, 4 and 8, the investigator as well as the patient assessed the overall response to treatment compared with the start of treatment as 1 = worse, 2 = unchanged, 3 = slight improvement, 4 = moderate improvement, 5 = marked improvement or 6 = clearance.

Assessment of tolerability

Facial skin irritation was assessed by localization to one or more of the following regions: forehead, periorbital region, cheek, nasolabial fold, chin, nose and ear. The severity of each of the following symptoms: burning, tenderness, itching; and signs: erythema, scaling, non-follicular papules, follicular papules was assessed as 0 = absent, 1 = mild, 2 = moderate or 3 = severe.

Skin irritation of the trunk and extremities was assessed by localization to one or more of the following regions: neck, axillae, chest, abdomen, upper back, lower back, genitofemoral folds, external genitalia, upper leg, knee, lower leg, foot, upper arm, elbow, forearm and hand. The severity of clinical symptoms/signs was assessed as 0 = absent, 1 = mild, 2 = moderate or 3 = severe. The clinical symptoms/signs recorded varied depending on the type of skin irritation. For irritation on treated lesions, the following symptoms: burning, tenderness; and sign: increased erythema were assessed with respect to severity. For irritation on perilesional skin (within a distance of 2 cm from a treated lesion), the severity of the following symptoms: burning, tenderness, itching; and signs: erythema, scaling, non-follicular and follicular papules was assessed. For patients with irritation on uninvolved skin (outside a distance of 2 cm from a treated lesion), the severity of the following symptoms: burning, tenderness; and signs: erythema, scaling, non-follicular and follicular papules was assessed.

Laboratory tests

At entry and at the end of treatment, blood samples were taken for the determination of serum calcium and serum creatinine. A pregnancy test was done at entry in all women of child-bearing age.

Statistical methods

The change and the percentage change in PASI from baseline to the end of treatment were normally distributed and were investigated by two-way analysis of variance classified by treatment and country, with PASI at baseline as covariate. If the variation between all four treatments was significant, the difference between the individual treatments was compared by Duncan's multiple range test in order to maintain the overall significance level of 5%. The assessment of overall response to treatment was investigated by a log-linear model of the contingency table classified by country, treatment and response, taking the ordering of the response $(1,\ldots,6)$ into account by using cumulative logits as response function in the model.

Skin irritation on a particular region and type of skin was counted only once within patients even if the irritation was recorded repeatedly, and the severity score of each symptom was taken as the maximum. The proportion of patients with irritation was compared between treatments by Fisher's exact test. The proportion of patients having adverse events and/or withdrawing because of some particular reason was compared between treatments by Fisher's exact test. All tests were two-sided with a 5% level of significance.

Results

A total of 699 patients were randomized: 174 to calcipotriol/vehicle (PASI 8·44); 174 to calcipotriol/calcipotriol (PASI 8·65); 175 to calcipotriol/clobetasone (PASI 8·11); and 176 to calcipotriol/betamethasone (PASI 8·45). The treatment groups were well matched at baseline with respect to sex, age, ethnic origin, skin type, duration of psoriasis, previous treatment of psoriasis (data not shown) and mean baseline PASI. The mean change in PASI was −3·86 (range −23·0 to 7·2) in the calcipotriol/vehicle group, −4·61 (range −33·5 to 10·2) in the calcipotriol/calcipotriol group, −4·61 (range −25·9 to 2·0) in the calcipotriol/clobetasone group and −5·03 (range −22·5 to 2·9) in the calcipotriol/betamethasone group. According to the mean change in PASI, calcipotriol/vehicle was significantly less effective ($P = 0{\cdot}02$) than the other three treatments, which did not differ from each other (Fig. 1A).

Assessed as the percentage change in PASI (Fig. 1B), a statistically significant difference was seen between the four treatment groups ($P = 0{\cdot}006$), with calcipotriol/vehicle being less effective than the other treatments, calcipotriol/calcipotriol being as effective as calcipotriol/clobetasone and calcipotriol/betamethasone being more effective than calcipotriol/calcipotriol. No difference was found between the calcipotriol/clobetasone group and the calcipotriol/betamethasone group (Fig. 1B).

According to the investigator's overall assessment of the treatment response, 28·5% of patients treated with calcipotriol/vehicle obtained either marked improvement or clearance. The corresponding values in the other treatment groups were 40·2% in the calcipotriol/calcipotriol group, 42·5% in the calcipotriol/clobetasone group and 54·0% in the calcipotriol/betamethasone group. These differences were not statistically significant ($P = 0{\cdot}20$). Correspondingly, 26·6% of patients treated with calcipotriol/vehicle obtained either marked improvement or clearance according to the patient's overall assessment. The values for the

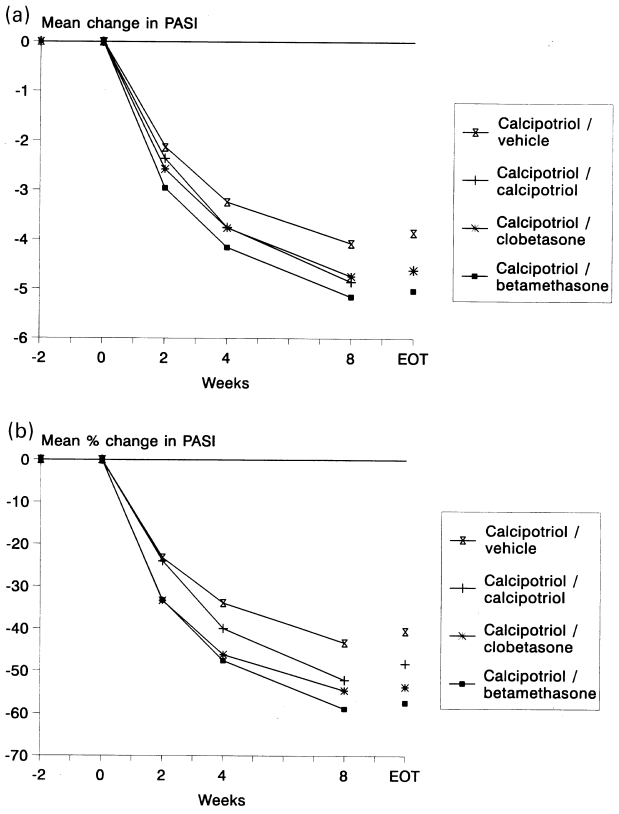

Figure 1. Mean change (A) and mean percentage change (B) in PASI from baseline (visit 2) to the end of treatment (EOT).

Table 1. Number of patients with skin irritation

	Calcipotriol/ vehicle ($n = 173$)	Calcipotriol/ calcipotriol ($n = 172$)	Calcipotriol/ clobetasone ($n = 172$)	Calcipotriol/ betamethasone ($n = 175$)	P[a]
Skin irritation					
Face	8	17	9	5	0·033
Treated lesions	39	44	28	22	0·009
Perilesional skin	12	21	7	8	0·011
Involved skin	6	7	6	5	0·94
Total number of skin irritations	65	89	50	40	
Total no. of patients (%)	54 (31·2)	59 (34·3)	41 (23·8)	30 (17·1)	0·001

[a]Chi-squared test.

other treatment groups were 40·1% in the calcipotriol/calcipotriol group, 40·1% in the calcipotriol/clobetasone group and 51·2% in the calcipotriol/betamethasone group. Statistical assessment showed treatment with calcipotriol/vehicle to be inferior and treatment with calcipotriol/betamethasone to be superior to the two other treatment regimens ($P = 0·04$).

The most frequent adverse event was skin irritation, which was reported in 31·2% of patients treated with calcipotriol/vehicle, 34·3% of patients treated with calcipotriol twice daily and 23·8% vs. 17·1% of patients treated with calcipotriol/clobetasone and calcipotriol/betamethasone, respectively (Table 1). Irritation of the face, treated lesions and perilesional skin was significantly different between the four treatment groups. Most skin irritation occurred in the calcipotriol/calcipotriol group, whereas both steroid combinations caused significantly less irritation (Table 1). Most skin irritation occurred on lesional skin, followed by the combination of lesional/perilesional skin and facial skin. Irritation of the facial skin was seen in 4·6% of patients treated with calcipotriol/vehicle, 9·9% of patients treated with calcipotriol twice daily, 5·2% of patients treated with calcipotriol/clobetasone and 2·9% of patients treated with calcipotriol/betamethasone. There were no significant differences between treatment groups in the severity of the skin irritation (data not shown). No body region seemed specifically sensitive to irritation. Treatment of flexural skin was allowed, and irritation in this location was rarely seen.

A total of 59 patients withdrew from the double-blind treatment (Table 2). Of these, 20 patients (2·9%) left the study because of adverse events, mainly skin irritation. No difference was seen between the treatment groups with respect to the amount of morning or evening

Table 2. Reasons for withdrawal from randomized treatment (primary reason recorded)

	Treatment			
	Calcipotriol/ vehicle ($n = 174$)	Calcipotriol/ calcipotriol ($n = 174$)	Calcipotriol/ clobetasone ($n = 175$)	Calcipotriol betamethasone ($n = 176$)
Adverse events	8	6	3	3
Medical deterioration	1	0	1	0
Unacceptable treatment response	2	3	0	1
Exclusion criteria	0	2	0	0
Lost to follow-up	6	3	3	5
Voluntary	1	2	0	1
Other reasons	0	0	4[a]	0
Unknown	1	1	1	1[a]
Total no. of patients	19	17	12	11

[a]Two reasons recorded for the same patient (two randomizations).

medication used. The amount of calcipotriol cream used in the calcipotriol/calcipotriol group averaged 36 g per week (range 1–117 g) over the 8-week treatment period. Mean serum calcium did not change during the study in any of the treatment groups, and no episodes of hypercalcaemia occurred (data not shown).

Discussion

The present study demonstrates that the combination of calcipotriol cream (50 μg/g) applied in the morning and vehicle cream applied in the evening for 8 weeks is effective in the treatment of psoriasis vulgaris. This treatment is, however, less effective than calcipotriol applied twice daily. Calcipotriol applied twice daily is as effective as calcipotriol/clobetasone and as effective as or less effective than calcipotriol/betamethasone, depending on the efficacy criteria considered.

In a previous study involving 8 weeks of treatment with either calcipotriol cream (50 μg/g) twice daily or betamethasone 17-valerate cream (0·1%) twice daily, the mean percentage reduction in PASI was similar in the betamethasone group (45·4%) and in the calcipotriol group (47·8%).[7] Another formulation of calcipotriol (ointment 50 μg/g) has also been compared with betamethasone 17-valerate ointment (0·1%) with percentage reductions in PASI ranging from 50·5% (betamethasone) to 61·2% (calcipotriol). Thus, the efficacy results in the current study are in good agreement with the results obtained in other clinical trials.

The incidence of skin irritation was less for patients treated with calcipotriol/corticosteroid compared with treatment with calcipotriol twice daily, whereas treatment with calcipotriol/vehicle did not reduce the incidence of skin irritation. Skin irritation was most common on lesional skin. Irritation of non-lesional facial skin was rare. Skin irritation was also subspecified according to the localization. No specific location on the face seemed to be particularly sensitive to irritation. On the body, irritation was most frequently recorded in the following regions: lower leg, knee and elbow. This may reflect the fact that psoriasis is often located in these areas rather than these areas being more sensitive to irritation. Because of its irritating potential, calcipotriol therapy is generally used with caution in skin folds. It is therefore remarkable that the irritation of skin folds was rather uncommon in the present study. This is, however, in accordance with the report that calcipotriol is well tolerated in the treatment of intertriginous psoriasis.[8] It can therefore be concluded that calcipotriol is well suited to the treatment of psoriasis lesions in skin folds.

In previous studies, calcipotriol has been applied twice daily. This is the first study comparing once-daily with twice-daily application. Although twice-daily application was superior, our results demonstrate that once-daily application may be sufficient for some patients. This is in accordance with the finding that calcipotriol ointment applied once daily is significantly better than its vehicle.[9] Unfortunately, once-daily application did not seem to reduce the incidence or severity of skin irritation.

Our results indicate that calcipotriol therapy combined with a medium-strength corticosteroid is sufficient to decrease skin irritation. To improve the efficacy, a potent corticosteroid appears to be required. However, even this combination offers only a slight additional efficacy. The superiority of the concurrent use of calcipotriol and a very potent corticosteroid is supported by the results of two studies using calcipotriol ointment. Thus, the calcipotriol/halobetasol combination applied for 2 weeks was more effective than either component alone.[10] Furthermore, the number of cutaneous adverse events was smaller in patients treated with the calcipotriol/halobetasol combination than with calcipotriol or halobetasol alone.[10] Furthermore, treatment with calcipotriol in the morning and betamethasone dipropionate in the evening was more effective and produced less skin irritation than calcipotriol twice daily after treatment for 6 weeks.[11] The present study did not include a group of patients treated with corticosteroid alone. The results from the study combining calcipotriol and halobetasol do, however, indicate that the combination therapy is more efficacious than the corticosteroid alone.

Although corticosteroids may decrease skin irritation and improve the efficacy of calcipotriol therapy, this does not imply that all psoriatic patients should use calcipotriol in combination with a corticosteroid. Thus, calcipotriol monotherapy induces marked improvement in many patients, and skin irritation is often mild and requires the cessation of therapy in very few patients.[12] Furthermore, topical corticosteroid therapy may be accompanied by other side-effects, in particular skin atrophy, during long-term use. It remains to be determined therefore to whom combination therapy should be offered. One approach is to use corticosteroid only in patients with a poor therapeutic response to calcipotriol. This idea is supported by a study in psoriatic patients with a 'low response' after 2 weeks of calcipotriol therapy.[13] In this selected group of patients, the concurrent use of betamethasone 17-valerate resulted in a greater antipsoriatic effect

compared with the continued use of calcipotriol twice daily.

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