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Comparative efficacy of calcipotriol (MC903) cream and betamethasone 17-valerate cream in the treatment of chronic plaque psoriasis. A randomized, double-blind, parallel group multicentre study

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Summary The efficacy, safety and tolerability of calcipotriol cream was compared with betamethasone 17-valerate cream in the treatment of plaque-type psoriasis in a multicentre double-blind, parallel group study. Patients with stable mild-to-moderate chronic disease were randomized to treatment with either calcipotriol, 50 μg/g, in a cream formulation (210 patients) or betamethasone 17-valerate cream, 1 mg/g (211 patients). After a wash-out period of 2 weeks, the treatment was applied twice daily, without occlusion, for 8 weeks or to complete clearing. The severity of psoriasis was assessed using the PASI at baseline and after 4 and 8 weeks treatment. The mean percentage reduction of PASI from baseline to end of treatment was 47·8% in the calcipotriol group and 45·4% in the betamethasone group. The reduction from baseline was highly significant in both groups, but the difference between the groups was not significant. There was a difference in the reduction in thickness of the lesions in favour of calcipotriol. The investigator's as well as the patient's overall assessment of treatment response at end of treatment showed no difference between the two treatment groups. Treatment-related adverse events were more frequent with calcipotriol than betamethasone. Lesional/perilesional irritation was reported in 16% and 9% ($P = 0·03$), and facial irritation in 10% and 0·5% ($P < 0·001$), respectively. No change was found in serum levels of calcium. Calcipotriol in a cream formulation was effective, safe, well-tolerated, and equal in effect to betamethasone valerate cream.

Calcipotriol (MC903), an analogue of vitamin D_3, has been shown to an be effective topical agent for treating psoriasis.[1,2] The first pilot clinical trial of calcipotriol used a cream formulation[1] but otherwise the published studies are with an ointment formulation. The objectives of the present investigation were to evaluate the efficacy, safety and tolerability of a stable calcipotriol cream[3] compared with betamethasone 17-valerate cream for plaque-type psoriasis.

Table 1. PASI at baseline in the two treatment groups, in per cent. The PASI can range from 0 to 64·8

PASI	Calcipotriol (group $n = 210$)	Betamethasone (group $n = 211$)
0– 5·9	58·1	60·7
6–10·9	30·5	26·1
11–15·9	9·5	10·0
16–20·9	1·4	2·4
>21	0·5	1

Materials and methods

Patients

A total of 435 patients were recruited for the study. Fourteen were withdrawn because they defaulted, left voluntarily, or did not comply with eligibility criteria. The resulting 421 patients were randomized either to treatment with calcipotriol (210 patients) or betamethasone valerate (211 patients). Outpatients aged 18 or over, of either sex, with a clinical diagnosis of stable mild-to-moderate plaque-type psoriasis on the limbs and/or the trunk were included. All patients had given signed informed consent. Patients were recruited at 41 dermatology centres in Finland (84 patients), Norway (90 patients), Sweden (138 patients) and the U.K. (109 patients).

The two treatment groups were well matched at baseline with respect to sex, age, race and severity of psoriasis as expressed by Psoriasis Area and Severity Index (PASI)[4] (Table 1). The extent of psoriasis at baseline was less than 10% of body surface in 70% of the patients, between 10% and 29% in 22% and more than 30% of the body surface in 7%. The lesions treated were evenly distributed on the upper and lower extremities and trunk. No facial or flexural lesions were treated.

Study design

The study design was a multicentre, prospective, randomized, double-blind parallel group comparison. The study was divided into two phases: a wash-out/qualification phase of 2 weeks, during which period only an emollient cream without salicylic acid was used if required, then a double-blind treatment phase lasting 8 weeks or to complete clearing. Intervals between control visits during treatment were 4 weeks. Cream containing calcipotriol 50 μg/g was compared with betamethasone 17-valerate cream 1 mg/g (0·1%). Both drugs were applied twice daily, without occlusion to psoriasis lesions, and lightly rubbed in.

Clinical assessment

The extent and severity of psoriasis lesions was assessed at each visit using the PASI. At control visits, investigators and patients gave their assessment of the overall response to the treatment as cleared, marked or slight improvement, no change or worse. Adverse events were elicited and recorded at all post-randomization visits.

Laboratory investigations

Samples of venous blood were obtained from patients at the first visit (recruitment) and end of treatment (or upon withdrawal). Serum assays for total calcium, phosphorus, albumin, bilirubin, alkaline phosphatase, aspartate aminotransaminase, alanine aminotransferase, and creatinine were performed.

Statistical analysis

The protocol required that all patients who were randomized in the study were accounted for in respect of efficacy and safety. Four patients left the study and defaulted after the first post-randomization visit so did not contribute any data to the analysis of efficacy and safety. The analysis of efficacy and of safety thus comprised 207 patients in the calcipotriol group and 210 in the betamethasone group. The basis for the sample size calculation was: the study should allow detection of a difference of 10% between the treatment groups with respect to mean change in PASI from baseline to end of treatment, further a standard deviation of 35% for the change in PASI from baseline to end of treatment. Therefore, 200 patients in each group should be enrolled in the study.

Results

Treatment response

The mean reduction in the PASI in patients treated with calcipotriol was 3·3 (95% confidence interval 2·9–3·7) and in patients treated with betamethasone 2·8 (95% confidence interval 2·3–3·3). The reduction in PASI was statistically highly significant in both treatment groups ($P < 0·001$) (Fig. 1). The difference between the two treatment groups with respect to change in PASI at the end of treatment was −0·5 (95% confidence interval

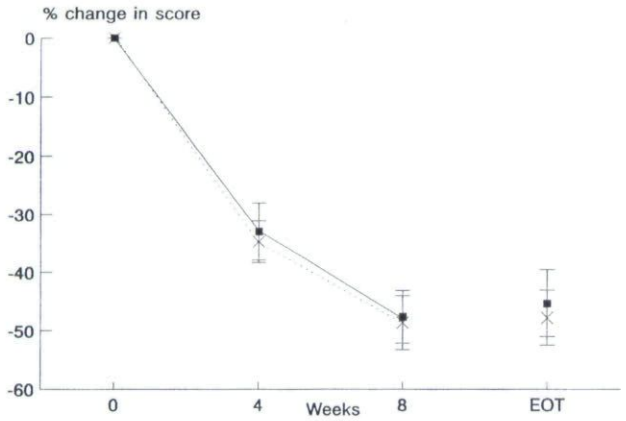

Figure 1. Percentage change in PASI from baseline to subsequent control visits and end of treatment (EOT) (mean value and 95% confidence interval). ■, betamethasone ($n = 209$, 201, 207 at 4 weeks, 8 weeks and EOT, respectively); ×, calcipotriol ($n = 207$, 196, 205, at 4 weeks, 8 weeks and EOT, respectively).

$-1{\cdot}2 \pm 0{\cdot}2$), which was not statistically significant ($P = 0{\cdot}17$). The mean percentage reduction in PASI from baseline to end of treatment was 47·8% and 45·4% in the calcipotriol and in the betamethasone groups, respectively ($P = 0{\cdot}51$).

There was a difference in reduction of thickness in favour of calcipotriol, which was statistically significant after 4 weeks of treatment ($P = 0{\cdot}04$), but not significant at end of treatment ($P = 0{\cdot}09$) (Fig. 2). In patients treated with calcipotriol, the mean reduction in thickness score from baseline to end of treatment was 2·59 (95% confidence interval 2·30–2·88), and with betamethasone 2·25 (95% confidence interval 1·97–2·52) ($P < 0{\cdot}001$). Similarly, the change in scores for redness and scaliness showed a highly significant reduction from

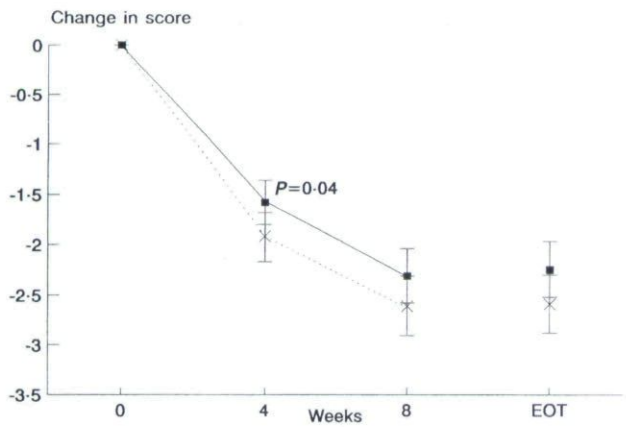

Figure 2. Change in whole body score for thickness from baseline to subsequent control visits and end of treatment (EOT) (mean value and 95% confidence interval). ■, betamethasone ($n = 209$, 201, 207 at 4 weeks, 8 weeks and EOT, respectively); ×, calcipotriol ($n = 207$, 196, 205, at 4 weeks, 8 weeks and EOT, respectively).

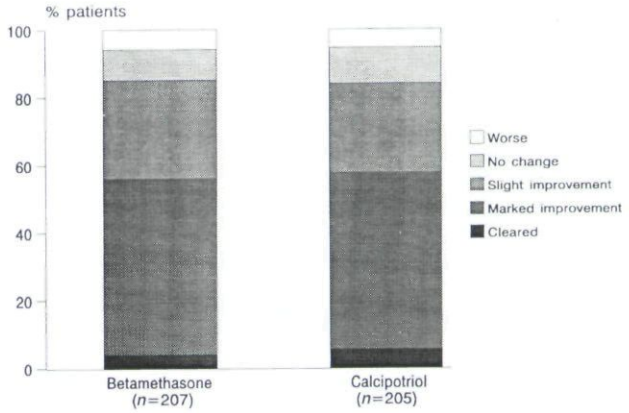

Figure 3. Investigator's overall assessment of treatment response at end of treatment. $P = 0{\cdot}90$.

baseline to end of treatment but there was no difference between calcipotriol and betamethasone groups.

The investigator's overall assessment of treatment response showed 58% of patients treated with calcipotriol cream cleared or achieved marked improvement as compared with 56% in the betamethasone group ($P = 0{\cdot}90$) (Fig. 3). The patient's overall assessment of treatment response at end of treatment mirrored that of the investigator.

A total of 21 (5%) of the 421 patients randomized in the study were withdrawn during the double-blind treatment period: 14 patients (6·7%) from the calcipotriol group and seven patients (3·3%) from the betamethasone group. The most frequent reason for withdrawal was adverse events: six patients in the calcipotriol group and three patients in the betamethasone group.

Tolerability and safety

Adverse events were more frequent with calcipotriol than betamethasone (Fig. 4). Lesional/perilesional irritation was the most common, reported by 16% in the calcipotriol group and 9% in the betamethasone group ($P = 0{\cdot}03$). Facial irritation occurred in 10% of patients treated with calcipotriol compared with only 0·5% treated with betamethasone ($P < 0{\cdot}001$). 'Epidermal thinning', 'atrophy of the skin', and 'translucency of the skin, early atrophy', were reported in three cases treated with betamethasone cream. Unacceptable adverse events (skin irritation) caused withdrawal of six patients on calcipotriol and three on betamethasone ($P = 0{\cdot}33$). No serious event was reported.

No significant change was found in serum calcium or in any other of the laboratory parameters during

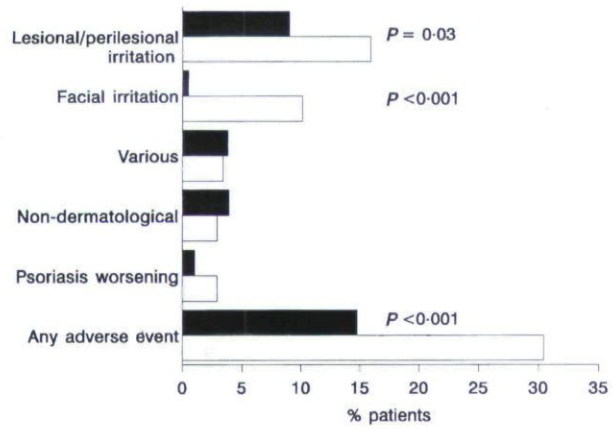

Figure 4. Percentage of patients who had adverse events recorded during treatment. ■, betamethasone ($n = 210$); □, calcipotriol ($n = 207$).

the treatment period. There was no evidence of hepatic or renal function being adversely affected by the treatments.

Discussion

The present study demonstrates that the effect of twice daily application of calcipotriol in a cream formulation was at least equally effective as betamethasone 17-valerate cream. Betamethasone was chosen as the control drug as it is an effective, well-tolerated and potent corticosteroid which, in many countries, is one of the most frequently prescribed corticosteroids for topical treatment in psoriasis. The clinical efficacy was measured using the PASI and the investigator's and the patient's overall assessment of therapeutic response. It can be argued that the PASI is not an ideal measurement of psoriasis because the area has a great influence on the index. However, the PASI is commonly used in clinical trials in psoriasis. It is of interest to note that, in this study, the reduction in thickness score with calcipotriol was significantly greater than with betamethasone after 4 weeks of treatment (but not at the end of treatment). The effect on redness is also of interest, as the reduction was equal with both treatments even though calcipotriol, unlike topical corticosteroids, has not been shown to have any vasoconstriction effect.

The reduction of thickness and redness imply that calcipotriol is at least as effective as betamethasone in the inhibition of both cell proliferation and inflammation. Similar results were also found in earlier studies using ointment formulations of calcipotriol and betamethasone in psoriasis.[5,6] The effect of calcipotriol on thickness was detectable within 1–2 weeks of topical application.[7] The findings are in accordance with the reported effect of calcipotriol, which results in a decrease of markers for epidermal proliferation,[8] which was significantly better than betamethasone.[9]

No formal trials have been published so far as regards the effect of betamethasone cream in psoriasis. All studies have been performed with betamethasone ointment formulations. Therefore, the treatment response to betamethasone cream in this study cannot be compared with others. However, the reduction of PASI after 6 weeks treatment with betamethasone ointment has been shown to be 62% in one recent right/left study,[5] and 52% in another study[6] which was a parallel group comparison. The reduction in PASI with calcipotriol ointment was 68% and 58% in the same studies, respectively. The reduction in PASI with calcipotriol cream in the present study corresponds well with the 48% reduction in PASI found in a previous study using calcipotriol in two cream formulations, one of which is the one used in the present study.[3]

No study has been performed comparing calcipotriol in ointment and in cream formulations, but comparisons across studies indicate that calcipotriol ointment seems to be somewhat more effective than calcipotriol cream. Therefore, a recommendation might be to use calcipotriol ointment in the early treatment of thick and scaly plaque lesions, in particular in the evening, followed by the cream when the lesions are thinner and less scaly. The cream may also be more cosmetically acceptable for daytime use.

The amount of calcipotriol cream used by the patients was not included in the present study. However, the maximal amount provided was 100 g/week, which has been shown to be safe in ointment formulations with respect to systemic calcium metabolism.[10,11]

There are no data available that show any difference in the transcutaneous resorption of calcipotriol in the ointment and cream formulations. It is, therefore, recommended that patients using calcipotriol cream adhere to the same guidelines as with calcipotriol ointment, regarding the amount used per week.

Lesional/perilesional irritation was the most common adverse event from calcipotriol, both in this study and in previous studies.[1,3,5,6] In the previous calcipotriol cream study,[3] the incidence of lesional/perilesional irritation was 11%, which is slightly less than the 16% in the present study. In a study of calcipotriol ointment, irritation was reported in 19%.[6] The lesional/perilesional irritation in the betamethasone group was as high as 9% in the present study, as compared with 4% in the ointment study.[6] Facial irritation was 10% in the

calcipotriol group in the present study, compared with 2% in the calcipotriol ointment study.[6] Almost no facial irritation was noted with betamethasone in either cream or ointment formulations.

In three cases, in the betamethasone group, thinning of the skin was reported at the end of treatment. Atrophy of the skin has not been reported with calcipotriol, even after prolonged treatment.[2]

In conclusion, calcipotriol in a cream formulation was effective, safe, well-tolerated, and equal in effect to betamethasone valerate cream.

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References

1 Kragballe K, Beck HI, Søgaard H. Improvement of psoriasis by a topical vitamin D_3 analogue (MC903) in a double-blind study. *Br J Dermatol* 1988; **119:** 223–30.

2 Kragballe K, Fogh K, Søgaard H. Long-term efficacy and tolerability of topical calcipotriol in psoriasis. *Acta Derm Venereol (Stockh)* 1991; **71:** 475–8.

3 Austad J, Goldin D, Harrington CI *et al.* Comparative effects of two different calcipotriol cream formulations versus placebo in patients with psoriasis vulgaris. *Proceedings of the 18th World Congress of Dermatology* New York City, June 12–18, 1992.

4 Fredriksson T, Pettersson U. Severe psoriasis—oral therapy with a new retinoid. *Dermatologica* 1978; **157:** 238–44.

5 Kragballe K, Gjertsen BT, de Hoop D *et al.* Double-blind, right/left comparison of calcipotriol and betamethasone valerate in treatment of psoriasis vulgaris. *Lancet* 1991; **337:** 193–6.

6 Cunliffe WJ, Berth-Jones J, Claudy A *et al.* Comparative study of calcipotriol (MC903) ointment and betamethasone 17-valerate ointment in patients with psoriasis vulgaris. *J Am Acad Dermatol* 1992; **26:** 736–43.

7 Kragballe K. Treatment of psoriasis by the topical application of the novel cholecalciferol analgue calcipotriol (MC903). *Arch Dermatol* 1989; **125:** 1647–52.

8 Jong de EG, Kerkhof van de PC. Simultaneous assessment of inflammation and epidermal proliferation in psoriatic plaques during long-term treatment with vitamin D analogue MC903: modulations and interrelations. *Br J Dermatol* 1991; **124:** 221–9.

9 Mare de S, Jong de EG, Kerkhof van de PC. DNA content and Ks8.12 binding of the psoriatic lesions during treatment with the vitamin D3 analogue MC903 and betamethasone. *Br J Dermatol* 1990; **123:** 291–5.

10 Mortensen L, Kragballe K, Wegmann E *et al.* Treatment of psoriasis vulgaris with topical calcipotriol has no short-term effect on calcium or bone metabolism. *Acta Derm Venereol (Stockh)* 1993; **73:** 300–4.

11 Bourke JF, Berth-Jones J, Iqbal SJ, Hutchinson PE. High-dose topical calcipotriol in the treatment of extensive psoriasis vulgaris. *Br J Dermatol* 1993; **129:** 74–6.