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Safety and efficacy of calcipotriol ointment (Dovonex®) in treating children with psoriasis vulgaris

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Summary Calcipotriol (Dovonex) ointment has been shown to be an effective, well tolerated, and acceptable treatment for psoriasis vulgaris in adults. This open study was conducted in 16 U.K. centres to assess the safety and efficacy of calcipotriol ointment in treating psoriasis vulgaris in children. Following a 2-week washout, patients were treated with calcipotriol ointment, 50 μg/g twice daily, for up to 8 weeks. A blood sample was taken on entry and a second 'on treatment' sample was taken after either 2 or 8 weeks treatment. Sixty-six children (26 boys, 40 girls, age range from 3 to 14 years) entered and 58 completed the study. There was a statistically significant reduction in the mean (±SD) Psoriasis Area and Severity Index (PASI) from 6·1 ± 3·5 at the start of treatment to 2·7 ± 1·9 at the end of treatment ($P < 0{\cdot}001$). Marked improvement or clearance of psoriasis at the end of treatment occurred in 65% of patients as assessed by the investigator and 62% as assessed by the patient. Cosmetic acceptability of calcipotriol ointment was found to be good or excellent in 79% of patients. Eight patients withdrew from the study (four defaulted, two unacceptable responses, two adverse events). Adverse events were reported by 16 patients; the most common being local irritation (seven patients). There was no significant change in the mean serum ionized calcium from baseline to 2 or 8 weeks treatment. Similarly, there were no consistent or clinically important changes in haematological, or other biochemical parameters, measured during the study period. Calcipotriol ointment has been shown to be an effective, well tolerated, and acceptable treatment for psoriasis vulgaris in children.

Calcipotriol is a vitamin D analogue which has been shown to be effective in the treatment of plaque psoriasis in adults.[1,2] In double-blind studies in adults it has proved equally effective to, or more effective than, betamethasone 17 valerate ointment (0·1%)[3,4] and more effective than short contact dithranol therapy in plaque psoriasis.[5] Although a theoretical risk, hypercalcaemia was not found in the recommended dose used in these studies, and calcipotriol has proved to be acceptable and safe in the treatment of adults with psoriasis. Psoriasis represents 4·1% of all dermatoses seen in children under the age of 16 years.[6] There has been no previous experience of calcipotriol treatment in children with psoriasis, and the purpose of the study was to confirm its efficacy and in particular to establish its safety and acceptability in this age group.

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Methods

Study design and subjects

A multicentre, prospective, non-controlled, open label trial of calcipotriol ointment (50 μg/g) was conducted in 16 hospital centres in the U.K. Children of either sex and age between 2 and 14 years, attending dermatology clinics for treatment of mild to moderate, stable, chronic plaque psoriasis on the arms, legs and trunk, but affecting less than 30% of body surface area, were recruited. Parents gave informed consent and the study was approved by the ethics committee at each centre.

Exclusion criteria were: systemic treatment or ultraviolet therapy during the 8 weeks preceding the study, ongoing osteoarthritic disease, abnormal renal or hepatic function, and hypercalcaemia. Children with acute guttate, pustular or erythrodermic psoriasis were excluded, as were those with predominant involvement of the face, flexures or scalp. Systemic therapy likely to affect the disease or laboratory parameters were prohibited during the study. These included calcium and vitamin D supplements, lithium, retinoids, diuretics, systemic steroids and antacids.

Subjects attended a pretreatment screening visit at which all treatment for psoriasis was discontinued, except for an emollient cream. After a 2-week washout period, subjects attended for a baseline visit and, assuming all entry criteria were met, were then included in the study, and were assessed at 2, 4, 6 and 8 weeks of active treatment.

Treatment and compliance

Calcipotriol ointment 50 μg/g (Dovonex®/Daivonex®) was applied twice daily, without occlusion, to all lesions (except for the face, scalp, genital region and areas covered by occlusive clothing, e.g. napkin, which was treated with the patient's usual topical medication). The amount of ointment used was determined using a nomogram that related the patient's height and weight to body surface area. Using the assumption that 30 g of ointment covers 0·2 m^2 for 14 applications per week, the maximum amount of ointment was calculated for each patient. Patients were given written treatment instructions and all tubes dispensed at each clinic visit were collected and weighed, to determine the amount of ointment used. New medication was prescribed at each visit.

Clinical assessment

At screening, baseline, and after 2, 4, 6 and 8 weeks treatment, the severity of psoriasis was assessed by the investigator using the Psoriasis Area and Severity Index (PASI) scoring system.[7] The head and neck were not assessed.

Overall efficacy assessment was undertaken by the investigator and the patient, after 2, 4, 6 and 8 weeks treatment using a five-point scale of: worse, no change, slight improvement, marked improvement, and cleared. An overall cosmetic acceptability assessment was made by the patient at week 8 and was rated as very poor, poor, acceptable, good or excellent. Overall efficacy assessment and acceptability assessment were made by the parents or legal guardians, if the child was under the age of 8. Adverse events were recorded at each visit.

Laboratory assessments and statistics

Full blood count, liver function tests, serum albumin, creatinine, ionized calcium and phosphate were undertaken at the time of screening. As blood sampling can be quite distressing to a child, this was minimized by randomizing the 'on treatment' blood sample to be taken either after 2 weeks, when more psoriasis would be present, or after 8 weeks, at the end of treatment, so that each child only had two venepunctures. Blood samples were taken using the Vacutainer® system and were analysed at a central laboratory (Hazleton Europe, Harrogate, U.K.).

The within patient changes in mean laboratory parameters, including ionized calcium, percentage changes in PASI and changes in elements of the PASI from baseline to subsequent visits, and to the end of treatment, were tested for statistical significance by one-sample *t*-tests. Before analysis, the distributions were checked to ensure the data were adequately represented by normal distributions, thus ensuring suitability of the *t*-test.

Results

Demographic data

Sixty-six children entered the study at 16 centres. There were 59 European Caucasians and seven Asians. There were 26 boys and 40 girls, mean age (±SD) 9·7 ± 2·8 years (range 3–14), and mean duration of psoriasis (±SD) 39·6 ± 33·9 months (range 2–144). The mean baseline PASI (±SD) was 6·1 ± 3·5 (range 1·4–18·9) Fifty-eight patients completed the study. Two patients withdrew because of adverse events (local irritation), two because of an unacceptable response to the calcipotriol ointment and four patients defaulted.

Compliance

The mean (±SD) duration of treatment was 7·7 (± 1·9) weeks (range 2·0–12·3 weeks). The mean (±SD) amount of ointment used was 16·9 (± 17·8) g/week (range 0·1–71·5), at the beginning of the study, which fell to 12·4 (±13·0) g/week (range 0·2–53·8) at the end of the 8 weeks treatment period. The overall

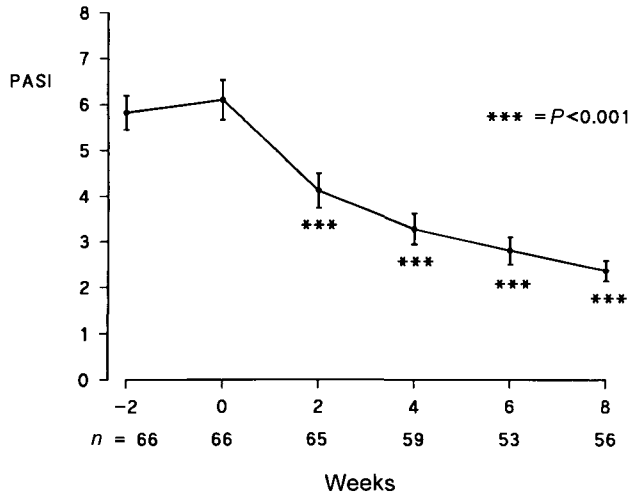

Figure 1. Mean PASI (± standard error of the mean) before and during treatment.

mean amount of ointment used per week, between the beginning and end of treatment was 15·0 g (range 0–71·5), which, when body surface area is taken into account, equates to less than 20 g/week per m^2 (range 0·15–45).

Response to treatment

During the study, the mean (±SD) PASI fell from 6·1 (± 3·5) at baseline to 2·4 (± 1·7) after 8 weeks treatment (Fig. 1). The mean percentage reduction in PASI between baseline and end of treatment was 51% ($P < 0·001$). There were significant reductions in the mean PASI after 2, 4, 6 and 8 weeks treatment, compared with the start of treatment. Similarly, there was a significant reduction in each individual component of the PASI (i.e. extent, redness, thickness and scaliness) at 2, 4, 6 and 8 weeks ($P < 0·001$). Overall efficacy assessment at the end of treatment showed clearance or a marked improvement in 65% of patients as assessed by the investigator, and 62% as assessed by the patient (Fig. 2). The overall cosmetic acceptability at the end of treatment was judged to be good or excellent by 50 patients (79%), and only one patient (1·6%) thought acceptability to be poor or very poor.

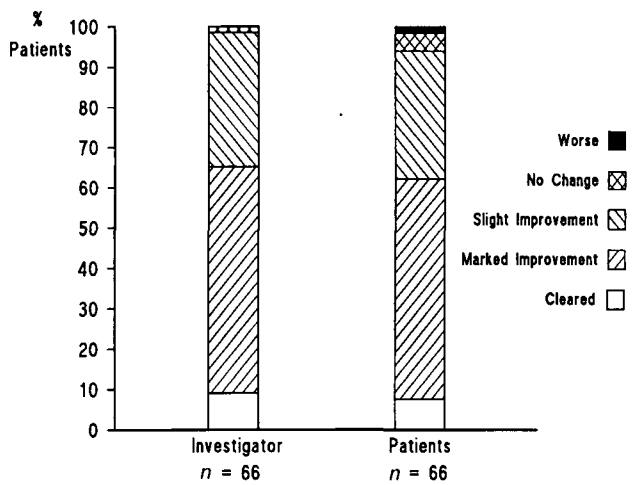

Figure 2. Patients' and investigators' overall efficacy assessment at the end of treatment.

Table 1. Adverse events

	n = 66	
	No.	%
Lesional/perilesional irritation	7	11
Irritation of face/scalp	4	6
Various skin rashes	4	6
Psoriasis worsening	1	2
Non-cutaneous	2	3
Total no. of adverse events	18	
Total no. of patients	16	24

Adverse events

No serious adverse events were reported. Sixteen patients (24%) reported, or were observed to have, a total of 18 adverse events, of which 15 were possibly or probably related to treatment (Table 1). Irritant reactions on or around the psoriatic lesion were the most common, and were noted in seven patients (11%), and facial irritation was seen in four (6%). Worsening psoriasis, necessitating withdrawal, was seen in one case. Non-cutaneous adverse events were recorded by two patients (chicken pox and influenza-like symptoms, which were judged to be unrelated to study medication).

Laboratory investigations

There was no significant change in the mean serum ionized calcium level from baseline to 2 weeks or 8 weeks treatment (Fig. 3). There was no correlation between the change in the serum ionized calcium and the amount of calcipotriol used. Similarly, there was no consistent or clinically important change in any haematological or other biochemical parameters measured.

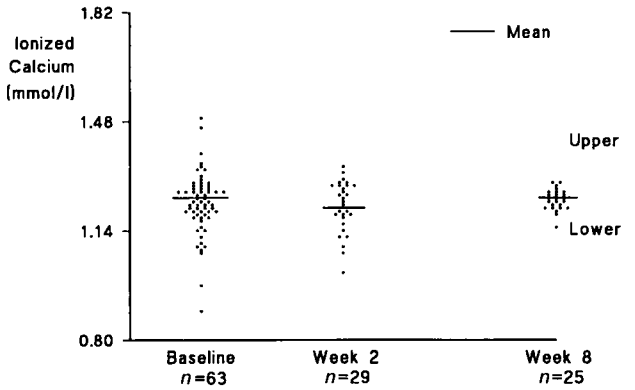

Figure 3. Mean serum ionized calcium from baseline to end of treatment.

Discussion

The benefit of calcipotriol is accepted in adults, and its efficacy is now confirmed in the treatment of children with chronic plaque psoriasis. There was a significant reduction in the mean PASI at each visit, compared with baseline. The reduction in the mean PASI in this study (51%) is slightly less than that seen in previous trials (58–59%) in which adults were treated with calcipotriol.[4,5] This is probably due to the lower baseline mean PASI score. The most rapid reduction occurred in the first 2 weeks of treatment. Most improvement is often seen when ointment is applied and scale is removed but the reduction in this case was seen following a 2-week washout period during which patients applied an emollient to their psoriasis lesions, so it was probably an effect of the treatment. Overall efficacy assessment by the investigator and patients were comparable, and marked improvement or clearance was seen in over 60%, as assessed by both. This response is again comparable with that seen in adult patients.[4] At the end of treatment, overall acceptability was good or excellent in 79% of patients.

No serious adverse events were reported or observed. Some irritation of lesional and perilesional skin is not uncommon, and occurs in approximately 20% of adult patients treated with calcipotriol.[4,5] Irritation was also observed in this study, but occurred in only 11% of children. Two of these children were withdrawn from treatment because of the irritation. Worsening of psoriasis while on treatment, in two children, and default in four, accounted for the other withdrawals from the study. Facial irritation or rash in patients being treated with calcipotriol is unexplained, but has been observed in other studies. It occurred in four children (6%), but was only a minor problem, and did not result in withdrawal from the study.

No significant change in serum ionized calcium levels were reported, and mean serum ionized calcium remained within the normal range during treatment. The amount of calcipotriol ointment used in this study was in the range of 0·15–45 g/week per m^2 body surface area. The use of calcipotriol in adults, up to a maximum of 50 g ointment/week per m^2, has not led to any problems with calcium or bone metabolism.[8] This study shows that use of up to 45 g/week per m^2, in children, does not seem to influence serum ionized calcium levels. One of the prime objectives of the present trial was to establish this aspect of the safety of calcipotriol in children.

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