EFFICACY AND SAFETY OF TOPICAL CHOLECALCIFEROL, CALCITRIOL, AND CALCIPOTRIOL IN THE TREATMENT OF PLAQUE PSORIASIS: A COMPARATIVE STUDY

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Abstract - The present work compared the clinical efficacy of topically applied vitamin D_3 (Cholecalciferol), 1α,25 - dihydroxy vitamin D_3 (calcitriol) with calcipotriol (Dovonex) in the treatment of plaque psoriasis. A randomized, double - blind, left - right, vehicle controlled study to assess the therapeutic efficacy and safety of twice daily application of 1 μg/g and 5 μg/g cholecalciferol, 1 μg/g calcitriol and 50 μg/g calcipotriol in 100 patients suffering from bilateral, symmetrical, moderate to severe plaque psoriasis was carried out. Twice daily calcitriol and calcipotriol significantly improved erythema, thickness, scaling and global severity of psoriatic plaques, and was much more effective than vehicle (10% hard paraffin in white soft paraffin), but the difference in clinical efficacy between cholecalciferol and vehicle was not statistically significant. On completion of study, clearance and marked improvement of psoriatic lesions was found in 4% of vitamin D_3 (1 μg/g) - treated, in 12% of vitamin D_3 (5 μg/g) - treated, in 48% of calcitriol (1 μg/g)- treated, and in 64% of calcipotriol (50 μg/g) - treated. Mean serum levels of total calcium, albumin - adjusted total calcium, phosphorus, creatinine, and also mean values of a 24 h urine calcium, phosphorus, creatinine, and mean urine calcium / creatinine ratio did not show clinically relevant changes in the baseline / end - point analysis. We conclude that topical - calcitriol and calcipotriol are effective and safe for the treatment of plaque psoriasis.

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Key words: Cholecalciferol, calcitriol, calcipotriol, vitamin D, psoriasis

INTRODUCTION

The use of vitamin D_3 and its analogues in the treatment of plaque psoriasis remain controversial (1). In the 1930s and 1940s vitamin D was given in extremely high doses for the treatment of a variety of skin disorders including scleroderma, eczema, acne, and psoriasis (2). It has been 50 years since high doses of oral vitamin D_2 were used for the treatment of psoriasis. The rational were based on the premise that the antipsoriatic effect of sun-light may be partly due to increased vitamin D_3 synthesis in the skin (3). Although some favorable responses were reported, the doses of vitamin D that was required to achieve these were so toxic that this therapeutic approach quickly lost favor (2). Vitamin D treatment was largely forgotten until a chance observation in 1985 that psoriasis got improved when a patient with osteoporosis was treated with oral 1α-hydroxy-vitamin D_3 (4). Fortunately molecular mechanisms and the new functions of vitamin D_3 were elucidated around the same time (5).

In the past decade, it has been recognized that receptors for 1,25 $(OH)_2$ D_3 are present, not only in classical target tissues such as the intestine, bone, and kidney, but also in a diversity of other tissues and cells including the parathyroid glands, pancreas, brain, gonads, pituitary gland, mononuclear cells, and activated T and B lymphocytes. The skin is not only the organ responsible for synthesizing vitamin D_3, but

also is one of the target organs for 1,25 $(OH)_2$ D_3. Receptors have been located in dermal fibroblasts, hair follicles, and in all of the layers of the viable epidermis (6). Epidermal keratinocytes produce vitamin D_3, metabolize it to its most biologically active form, 1,25 - dihydroxy vitamin D_3, and respond to 1,25 $(OH)_2$ D_3, with a decrease in proliferation and increase in differentiation (7).

The ability of calcitriol to modulate the proliferation of T-lymphocytes (8, 9) may also be important for the antipsoriatic effect of calcitriol.

Although the natural form of vitamin D_3, 1,25 $(OH)_2$ D_3 , used either orally (10) or topically (11, 12) improves psoriasis, there has been an interest in developing vitamin D analogues that separate the newly identified effects from the classic hypercalcemic effect. Tacalcitol (1,24$(OH)_2$ D_3) (13) and calcipotriol, which is called calcipotriene in the USA (14), are currently the most promising analogues. But calcipotriol has been studied most extensively and is the only vitamin D analogue that has reached the market.

The aim of the study reported here was to assess the safety, tolerance, efficacy and comparative study of cholecalciferol (1 μg/g and 5 μg/g), calcitriol (1 μg/g), and calcipotriol (50 μg/g), applied twice daily to skin lesions in patients with moderate to severe psoriasis.

MATERIALS AND METHODS

Ointment Formulation

We used Rocaltrol® capsules 0.25 μg calcitriol as a source of Rocaltrol ointment.

Previously, we have removed the capsule contents by aspiration with needle and syringe. This is a tedious process and presents problems with accurate quantitative removal of the oily calcitriol solution. A mean of accurately formulating calcitriol ointment is made by water/oil extraction of Rocaltrol® capsules and a subsequent assessment of stability of the topical preparation. Calcitriol ointment in a strength of 1 μg/g in petrolatum base (10% hard paraffin in white soft paraffin) was formulated by dispersing 100 Rocaltrol® capsules in 80 ml of distilled water warmed to 35°C. The dispersion was divided into two polypropylene 50ml capacity centrifuge tubes and centrifuged at ambient temp for 15 min at 3000 g. The upper oily layer (medium chain triglyceride containing lipophilic calcitriol was carefully pipetted off and added to a previously tared procelain slab and sufficient ointment base added to a final weight (25 g in the case of a 1 μg/g ointment). As much as practical all steps were protected from light with aluminium foil (15).

For cholecalciferol ointment, vitamin D_3 capsules (Merck, 50000 IU), and for calcipotriol ointment, Dovonex® 50 μg/g ointment (Leo laboratories limited - Ireland) were used.

Patients

One hundred patients with moderate to severe plaque psoriasis, involvement not exceeding 40% of their body surface area, with no other significant illness, were recruited (Table 1). They had not responded satisfactorily to at least one of the standard treatments for psoriasis. Women with child-bearing potential, pregnant women and nursing mothers, and patients with hepatic or renal impairment or idiopathic hypercalciuria, were excluded. They received no topical treatment for at least 4 weeks, or systemic treatment for at least 2 months, prior to entering the study. All patients gave informed consent after a full explanation of the details, procedures and potential risks of the study.

Protocol

They were included in a placebo - controlled, double blind, left-right, comparative study of cholecalciferol, calcitriol and calcipotriol. 25 patients were treated twice daily for 4 months with cholecalciferol ointment (1 μg/g), 25 patients were treated twice daily for 4 months with cholecalciferol ointment (5 μg/g), 25 patients were

treated twice daily for 3 months with calcitriol ointment (1 μg/g), and 25 patients were treated twice daily for 2 months with calcipotriol ointment (Dovonex® 50 μg/g). 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 30g 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 tubs dispended at each clinic visit were collected and weighed, to determine the amount of ointment being used. New medication was prescribed after each visit.

Evaluation of Patients

Patients were seen at 1, 2, 4, 8, 12, 16 weeks. At baseline and at each subsequent visit the investigator assessed the extent of involvement and severity of the lesions with respect to erythema, scaling, and thickness. Severity was assessed on a 5-point scale and graded as follows: most severe (4), severe (3), moderate (2), slight (1), none (0). These assessments were used to calculate a modified Psoriasis Area and Severity Index (PASI) score (16). At each control visit, the investigator recorded the response to treatment as follows: Clearance or marked improvement (+3), moderate improvment (+2), minimal improvement (+1), no change (0) and worse (-1). Each patient also assessed the response to treatment on a similar basis.

Laboratory Studies

Samples of venous blood were obtained from patients before and at viarious intervals during the study. Serum assays for total calcium, phosphorus, creatinine, urea, alcaline phosphate, albumin, serum glutamic pyruvic transaminase (SGPT), serum glutamic oxaloacetic transaminase (SGOT), uric acid, cholesterol, and also urine calcium, phosphorus and creatinine were analyzed.

Statistical Analysis

Statistical significance was assessed within groups by the two-tailed Student's t-test for paired differences. Results are expressed as the mean ± standard deviation (SD). All results were considered significant at $P<0.05$.

RESULTS

The mean (± SD) duration of treatment with calcipotriol (50 μg/g) ointment was 1.8 ± 0.8 months (range 0.6 - 2.8 months), with calcitriol (1 μg/g) ointment was 2.5 ± 0.4 months (range 1.5 - 3.4 months), with cholecalciferol (5 μg/g) ointment was 3.4 ± 0.7 months (range 2.6 - 4.1 months), and with cholecalciferol (1 μg/g) ointment was 3.5 ± 0.5 months (range 2.9 - 4.6 months). At baseline (week 0), the four treatment groups were similar regarding the distribution of variety of characteristics (Table 1). All patients completed the study.

All patients experienced an improvement in their lesions on the calcipotriol and calcitriol-treated side. But the difference in clinical efficacy between cholecalciferol and vehicle was not statistically significant. After 1 week of calcipotriol treatment and after 2 weeks of calcitriol treatment, we found less erythematous, thinner and fine scaled plaque on the calcipotriol and calcitriol than on the placebo - treated side, lesions continued to improve there after so that, at the end of the trial, only a residual mild erythema was detectable on the calcipotriol and calcitriol-treated plaques whereas no or minimal improvement was seen in the placebo-treated ones.

Clearance or marked improvement observed in 1 patient (4%) was treated with 1 μg/g cholecalciferol ointment, in 3 patients (12%) treated with 5 μg/g cholecalciferol ointment, in 12 patients (48%) treated with 1 μg/g calcitriol ointment, and in 16 patients (64%) treated with 50 μg/g calcipotriol ointment (Table 2).

The four groups were compared with respect

Table 1. Dermographic data and disease characteristics of evaluable patients, values are mean ± SD (standard deviation) and ranges.

Characteristics	Cholecalciferol 1 μg/g	Cholecalciferol 5 μg/g	Calcitriol 1 μg/g	Calcipotriol 50 μg/g
Sex	15 M 10 F	9 M 16 F	14 M 11 F	16 M 9 F
Age (years)	35.2 ± 14.8	36.1 ± 17.5	34.9 ± 18.6	37.1 ± 18.4
	(10.2 - 58.7)	(7.1 - 62.3)	(6.2 - 64.1)	(8.3 - 69.1)
Duration of	11.3 ± 6.3	15.2 ± 9.8	13.7 ± 9.6	15.3 ± 9.8
psoriasis(years)	(4.6 - 24.0)	(2.5 - 39.3)	(2.2 - 32.5)	(3.5 - 35.5)
Percentage body	19.4 ± 5.2	21.9 ± 5.8	23.2 ± 7.2	23.6 ± 8.9
surface involved	(10.2 - 36.7)	(15.2 - 32.1)	(14.5 - 40.0)	(12.7 - 40.0)
Clinical scores	2.5 ± 0.4	2.5 ± 0.5	2.6 ± 0.4	2.7 ± 0.3
Erythema	(1.4 - 3.0)	(1.5 - 3.1)	(1.7 - 3.2)	(1.6 - 3.1)
Thickness	2.4 ± 0.6	2.5 ± 0.4	2.4 ± 0.5	2.5 ± 0.5
	(1.3 - 3.2)	(1.6 - 3.0)	(1.6 - 3.1)	(1.5 - 3.2)
Scaling	2.1 ± 0.6	2.2 ± 0.6	2.3 ± 0.5	2.3 ± 0.4
	(1.3 - 3.0)	(1.3 - 3.0)	(1.6 - 3.1)	(1.5 - 3.1)

to PSAI at baseline, and comparison was performed between the side of the patients classified by treatment. No statistically significant difference in mean PSAI was found between

Table 2. Distribution of patients over the global improvement scale at the end - point.

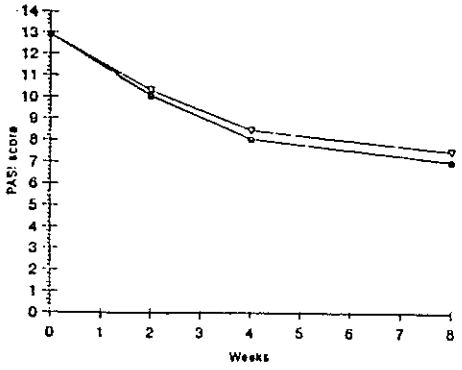
Ointment	n	-1	0	+1	+2	+3
Cholecalciferol(1 mg/g)	25	---	4	8	12	1
Vehicle		---	7	10	8	---
Cholecalciferol(5 mg/g)	25	---	1	7	14	3
Vehicle		---	5	9	11	---
Calcitriol(1mg/g)	25	---	---	4	9	12
Vehicle		---	3	10	12	---
Calciptriol(50mg/g)	25	---	---	1	8	16
Vehicle		---	2	8	15	---

1, worsening; o, no change; +1 minimal improvement., +2, moderate improvement., + 3, clearances or marked improvement., n, the number of patients.

cholecalciferol and placebo-treated. However significant difference were seen in mean PASI between calcitriol and placebo-treated, andbetween calcipotriol and placebo - treated (Table 3, Figs. 1, 2, 3, 4). In both groups there was stati- stically significant reduction in PASI at all time points, and the greatest reduction was during the first 2 weeks. There were highly significant difference in favor of calcipotriol and calcitriol for the reduction in the scores for erythema, thickness and scaling after 2 and 4 weeks of treatment. Both investigators and patients judged the overall clinical response to calcipotriol and calcitriol to be superior to a placebo ($P<0.001$). The preference for calcipotriol and calcitriol was highly significant.

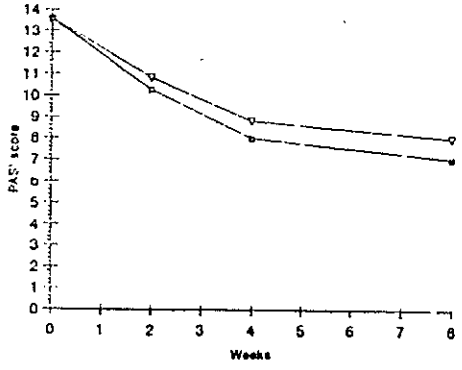
Histological examination of the skin biopsy taken from cholecalciferol and placebo - treated plaque of the patient revealed focal para-keratosis, an intracorneal neutrophilic infiltrate, psoriasiform epidermal hyperplasia, hypo-granulosis, dermal papillary oedema, telangiectasia, and a superfacial perivascular lymphocytic infiltrate. These changes are typical of psoriasis.

In contrast, the skin biopsy of the lesion treated with topical calcitriol and calcipotriol showed orthokeratosis, a marked reduction in



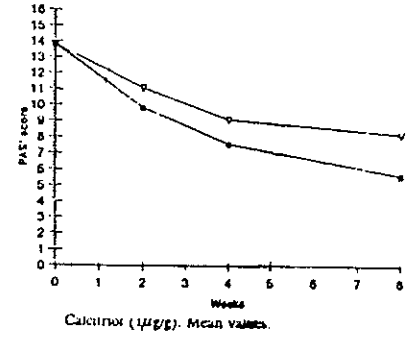
□ Cholecalciferol 1 μg/g., ▽, Vehicle

Fig. 1. change in PASI during 8 - weeks treatment of cholecalciferol (1 μg/g). Mean values.



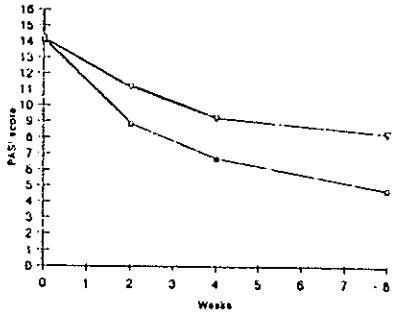
□ Cholecalciferol 5 μg/g., ▽, Vehicle

Fig. 2. change in PASI during 8 - weeks treatment of cholecalciferol (5 μg/g). Mean values.



□ Calcitriol 1 μg/g., ▽, Vehicle

Fig. 3. change in PASI during 8 - weeks treatment of Calcitriol (1 μg/g). Mean values.



□ Calcipotriol 50 μg/g., ▽, Vehicle

Fig. 4. change in PASI during 8 - weeks treatment of Calcipotriol (50 μg/g). Mean values.

epidermal thickness, a prominent granular layer without a neutrophilic infiltrate, and minimal perivascular lymphocytic infiltration.

No serious adverse events were reported. Irritant reactions on or around the psoriatic lesion were the most common, and were noted in 5 patients (20%) treated with calcitriol ointment but in 11 patients (44%) treated with calcipotriol ointment, and facial irritation was seen in 3 patients (12%) treated with calcipotriol ointment.

No statistically significant and clinically relevant changes were observed in the baseline/end-point analysis of any laboratory parameter. Blood biochemistry baseline/end-point analysis for calcium, albumin-adjusted calcium, phosphorus, creatinine, and the mean values of 24 h urine calcium, phosphorus, creatinine, urine calcium/creatinine ratio and creatinine clearance did not show clinically relevant in the baseline/end-point analysis. The mean systolic/ diastolic blood pressure and mean pulse rate also remained well within the normal range throughout the study and baseline/end-point analysis did not reveal any clinically relevant

Table 3. Change in PSAI during 8 - weeks treatment. Values are mean ± SD

	Cholecalciferol		Cholecalciferol		Calcitriol		Calcipotriol	
	1 μg/g	Vehicle	5 μg/g	Vehicle	1 μg/g	Vehicle	50 μg/g	Vehicle
Baseline	12.92 ± 5.89 (2.9-20.81)	12.91 ± 5.90 (2.88-20.70)	13.56 ± 5.69 (4.25-22.54)	13.57 ± 5.68 (4.30-22.50)	13.82 ± 7.15 (3.73-24.19)	13.81 ± 7.16 (3.55-24.10)	14.11 ± 5.2 (4.60-25.10)	14.20 ± 5.1 (4.70-25.15)
After 2 weeks	10.08 ± 5.59	10.33 ± 4.60	10.30 ± 4.02	10.86 ± 5.84	9.81 ± 5.60	11.05 ± 7.11	8.90 ± 3.40	11.20 ± 4.76
After 4 weeks	8.06 ± 4.67	8.47 ± 3.07	8.03 ± 3.37	8.84 ± 5.93	7.56 ± 4.23	9.06 ± 6.02	6.72 ± 2.91	9.24 ± 4.36
After 8 weeks	7.05 ± 4.27	7.52 ± 2.48	7.07 ± 2.47	8.05 ± 5.62	5.62 ± 3.74	8.15 ± 6.24	4.75 ± 2.68	8.28 ± 4.72
	Difference between Treatment		Difference between Treatment		Difference between Treatment		Difference between Treatment	
After 2 weeks	0.26 ± 1.21		0.39 ± 1.42		1.24 ± 1.30		2.32 ± 1.85	
After 4 weeks	0.35 ± 1.45		0.79 ± 2.72		1.47 ± 1.45		2.52 ± 1.95	
After 8 weeks	0.38 ± 1.51		0.97 ± 3.03		2.51 ± 2.41		3.52 ± 2.66	
n	25		25		25		25	
P value	NS		NS		NS		0<0001	

n, number of patients., NS, not significant

changes in these parameters. Topical cholecalciferol, calcitriol, and calcipotriol withdrawal was not followed by rebound phenomena in any patients, whereas in all patients treated with cholecalciferol, 2 patients (8%) treated with calcitriol, and 4 patients (16%) treated with calcipotriol the disease relapsed within some variable intervals.

DISCUSSION

Only a few short-term studies have been conducted to evaluate the efficacy of topical and oral calcitriol. These short-term studies have suggested that calcitriol can be an effective therapy for the treatment of psoriasis (17,18). The study of 85 patients using oral calcitriol revealed that 88.0% of patients had improvment in the activity of their disease (17). Ten ch leren affected by psoriasis, using topical calcitriol and after 4 weeks all childeren showed a complete clearing of their skin lesions (19).

This study demonstrates that calcitriol and calcipotriol ointment are effective antipsoriatic drugs in patients with moderate to severe disease. In most patients, the antipsoriatic effect of 1 μg/g calcitriol ointment applied twice daily was obvious after treatment for 2 weeks and continued to develop throughout 12 - weeks treatment period, but the antipsoriatic effec of 50 μg/g calcipotriol

ointment applied twice daily was obvious after treatment for 1 week and continued to develop throughout the 8-weeks treatment period.

The ointment containing cholecalciferol at a concentration of 5 μg/g was slightly superior to that containing 1 μg/g, but the difference in clinical efficacy between cholecalciferol ointment and vehicle was not statistically significant.

The degree of improvement obtained with 50 μg/g calcipotriol ointment was much higher than that produced by the 1 μg/g calcitriol ointment. The reason for this may be that calcitriol ointment contained lower concentration of the active ingredient than the calcipotriol ointment. Because calcitriol is calciotropic, attempts to raise concentration might produce hypercalcemia. Mac Louglin and coworkers (20) in 1985 reported that cultured psoriatic fibroblasts had a partial resistance to the differentiating activity of 1α-25 $(OH)_2D_3$. He predicted that cultured psoriatic keratinocytes also would have a partial resistance. This finding prompted several clinical studies using oral or topical administration of vitamin D metabolites in the treatment of psoriasis.

In 1986, Morimoto and coworkers (21) conducted the first in vivo study involving three different groups. Their open study concluded that oral vitamin D may be effective in treating psoriasis and that 1α - hydroxy -vitamin D_3 seemed to be more effective than calcitriol. Their results also suggested that topical calcitriol was effective in psoriasis

In 1988, Smith and coworkers (22) reported similar results. Ten of 14 patients treated with oral vitamin D showed at least moderate improvement after six to eight months of therapy.

Furthermore, the authors found topical calcitriol to be safe and effective for treating psoriasis in localized areas.

In 1989, Van de Kerkhof and coworkers (23) found insufficient evidence of the clinical efficacy of topical calcitriol. Ten patients selected for experiment applied calcitriol 1 μg/g of medium-chain triglyceride (MCT) base to one lesion and placebo to the contralateral lesion twice daily for 28 days. No occlusions were done.

They suggested that the application of calcitriol without plastic occlusion may have resulted in insufficient bioavailability of the drug. Another possible explanation for the ineffectiveness of calcitriol may be the base used. Petrolatum base has been shown to stimulated epidermal growth and to alter epidermal cells so that they can respond to vitamin D.

Another study agreed with the findings of Van de Kerkhof and coworkers. Henderson and coworkers studied 47 patients with chronic stable psoriasis. Two psoriatic plaques were chosen from each patient, one was treated daily with calcitriol 0.5 μg in 25 ml of MCT base for four weeks, whereas the other was treated with MCT base only. Twenty-one patients treated with calcitriol plus base showed greater improvement compared with ten patients treated only with the base. However, this result was not significant.

In 1989, Kragfalle (24) reported a study using topical application of a synthetic cholecalciferol analogue named calcipotriol. He treated 50 patients with psoriasis and found improvement in 63% of them when using a 50 μg/g ointment.

In conclusion, this study demonstrated that twice daily application of 1 μg/g calcitriol ointment and 50 μg/g calcipotriol ointment is safe and well tolerated in the treatment of moderate to severe plaque psoriasis.

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