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Treatment of Psoriasis Vulgaris with Topical Calcipotriol Has No Short-term Effect on Calcium or Bone Metabolism

A Randomized, Double-blind, Placebo-controlled Study

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The purpose of this double-blind, placebo-controlled study was to examine whether the vitamin D analogue calcipotriol, topically applied to psoriatic skin lesions, had any effect on calcium or bone metabolism. Thirty-four outpatients with psoriasis vulgaris were randomized to treatment with either calcipotriol ointment (50 μg/g) or vehicle ointment twice daily for 3 weeks. The patients were put on a calcium energy fixed diet and examined once weekly. The mean amount of calcipotriol ointment used was 40.3 g/week (range 8.2–95.4 g/week). The results of biochemical markers on calcium and bone metabolism showed no significant differences between the two groups. No correlation was found between the amount of ointment used and changes in parameters on calcium and bone metabolism during the 3-week treatment. It is concluded that calcipotriol ointment (50 μg/g), applied in doses of 8.2–95.4 g/week for 3 weeks to psoriatic skin lesions, has no effect on calcium or bone metabolism. ***Key word: Vitamin D.***

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In 1987 the synthesis of a new vitamin D analogue, calcipotriol (MC903), was reported (1). The in vitro effects of calcipotriol on keratinocytes are similar to those of 1,25-dihydroxyvitamin D_3, $1,25(OH)_2D_3$, the physiologically active form of vitamin D (2–4), and its therapeutic efficacy on psoriasis vulgaris has since then been documented in several studies (5–8). The advantage of calcipotriol over $1,25(OH)_2D_3$ is its low calcemic potential due to a much higher clearance rate (9) and low absorption from skin surface (10). In earlier clinical studies with calcipotriol ointment, patients were allowed to use up to 100 g ointment per week, and serum-calcium was within normal range, and unchanged, during all studies. However, 2 case stories of hypercalcemia after excessive use of calcipotriol ointment for extensive psoriasis have been reported (7, 12). One of these 2 patients had decreased renal function.

Earlier studies have shown that $1,25(OH)_2D_3$ is effective in the treatment of psoriasis vulgaris (13–15). Receptors for $1,25(OH)_2D_3$ have been shown on keratinocytes, and $1,25(OH)_2D_3$ inhibits proliferation and induces differentiation in keratinocyte cultures (16–18). The use of $1,25(OH)_2D_3$ and other bioactive forms of vitamin D in the treatment of psoriasis is limited by their potentially hypercalciuriatic effect (19). Studies on both topically and orally applied $1,25(OH)_2D_3$ have shown that the treatment results in hypercalciuria (20, 21). $1,25(OH)_2D_3$ increases serum-calcium by increasing intestinal calcium absorption and renal calcium reabsorption (19). $1,25(OH)_2D_3$ exerts a negative feed-back regulation on the production of parathyroid hormone (PTH). It also has an effect on bone metabolism. Receptors for $1,25(OH)_2D_3$ have been demonstrated in osteoblasts, but not in osteoclasts (22–24). $1,25(OH)_2D_3$ stimulates the osteoblasts, both number and activity, resulting in accelerated bone formation. The stimulation of osteoblasts increases synthesis of osteocalcin and alkaline phosphatase and collagen formation, but the reason and consequences are still not fully clarified. $1,25(OH)_2D_3$ also increases bone resorption, in part by stimulation of secretion of cytokines, which stimulates osteoblast differentiation (25, 26).

The aim of this study was to examine whether calcipotriol ointment (50 μg/g), used in recommended doses, up to 100 g per week, has any effect on calcium and bone metabolism evaluated by specific biochemical markers.

MATERIAL AND METHODS

Study design

The study was designed as a double-blind placebo-controlled study. The patients were randomized for treatment with either calcipotriol ointment (50 μg/g) or placebo (vehicle) ointment, up to 100 g/week. The patients were treated for 3 weeks. No other treatment for psoriasis was permitted during the study period. The ointment was applied twice daily to all psoriatic lesions, followed by hand-washing. In order to exclude the food-induced changes in calcium metabolic parameters, the patients were kept on a calcium and energy fixed diet for 4 days prior to the weekly examination. The diet was designed by a dietician on the basis of an individual 4-day dietary diary, so that the diet matched the patients' usual daily calcium and energy intake. At the start of the study and once a week for the following 4 weeks, the patients collected a 24-hour urine sample on the 4th day on diet. Clinical and biochemical examinations were performed at the start of treatment and then once weekly for the following 4 weeks, after fasting and at the same time of the day every time.

Subjects

The patient group consisted of adult outpatients suffering from stable, plaque-type psoriasis vulgaris. The psoriatic lesions covered 5–33% of the body surface. Patients with guttate or pustular psoriasis or with psoriasis in unstable phase were not allowed to participate. The patients had no diseases, including psoriatic arthritis, which could influence calcium or bone metabolism and received no medication with known influence on calcium or bone metabolism (including diuretics, hormones, antipileptics, corticosteroids, calcium or strong vitamin D supplementation). All patients had normal renal and hepatic functions. No one had been exposed to artificial UV radiation or sunbathing for at least 2 months before inclusion in the study. The study took

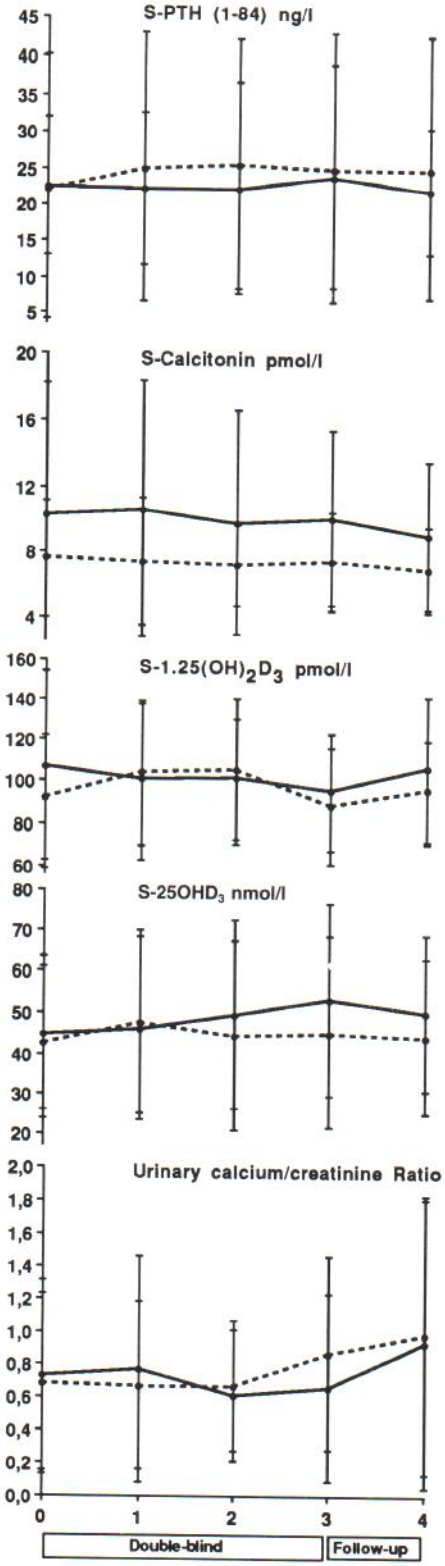

Fig. 1. Serum and urinary markers of calcium metabolism (mean and SD). * = $p \leq 0.05$. (——) = Calcipotriol group, $n = 17$. (----) = Placebo group, $n = 17$.

place outside the summer season. Any topical treatment for psoriasis was stopped at least 2 weeks before inclusion.

Clinical assessment

Psoriatic activity was assessed according to the PASI system (Psoriasis Area and Severity Index) (27), and overall assessment compared to baseline value was obtained from both patients and the investigator.

Biochemical examinations

At all visits the following parameters on calcium metabolism were estimated: serum-CA(ionised) (at standard pH), serum-phosphate, serum-alkaline phosphatase, serum-parathyroid hermone (S-PTH(1–84)), serum-calcitonin, serum-25(OH)D_3, serum-1,25$(OH)_2D_3$. The 24-hour urine sample was analysed for calcium, phosphate and creatinine.

Bone metabolism was monitored by the following parameters: serum-bone alkaline phosphatase, serum-osteocalcin and serum-carboxyterminal propeptide of type I procollagen (S-PICP) as markers of osteoblast function (28, 29, 33, 34) and serum-carboxyterminal pyridinoline crosslinked telopeptide parts of type I collagen (S-ICTP) as marker of osteoclast function (31, 32).

The serum PTH(1–84) was measured by an immunoradiometric assay (Allegro Intact PTH, IRMA from Nichol's Institute, San Juan, Capistrano, California, USA), intraassay coefficient of variance (CV) = 2.6%, interassay CV = 5.8%. Serum-calcitonin was measured by a radioimmunoasay (28). The vitamin D metabolites were separated by HPLC, after extraction with acetonitrile, and then measured by competitive protein binding assays (routine method, Dept Clin Chem, Randers Centralsygehus, Denmark). Urine calcium was measured by atomic absorption spectrophotometry after acidification of urine (standard laboratory methods). The bone alkaline phosphatase was analysed spectrophotometrically (30); after lectin precipitation, the interassay CV was 25% and the intraassay CV 8% (29). The osteocalcin was determined by a radioimmunoassay using rabbit antisera against bovine BGP, with an interassay CV = 10% and intraassay CV = 5% (33). The S-PICP was measured by a radioimmunoassay from Orion Diagnostica (Oulunsalo, Finland) (34); the interassay CV was 5% and the intraassay CV 3%, and the detection limit = 1.2 ug/l. The S-ICTP was analysed by an equilibrium radioimmunoassay, the inter- and intraassay CV being approximately 5% (31).

Serum samples were analysed for calcipotriol using a competitive protein binding assay after sample purification by solid phase extration and normal phase HPLC (H Sorensen, Analytical-Chemical Research Department, Leo Pharmaceutical Products, Ballerup, Denmark), detection limit = 50 pmol/l. The weekly amount of ointment applied was registered.

Statistics

The study was planned to include at least 2 × 16 patients. This was based on calculations assuming a 20% inter-patient standard deviation of change in 24-hour urinary excretion of calcium and a power of 80% to detect a difference between groups of 20% on a 5% level of significance.

Comparisons between groups in respect of laboratory parameters and of PASI were based on a two-sample *t*-test. Intra-group changes were evaluated by a one-sample *t*-test. Correlation between amount of ointment used and change in laboratory parameters was evaluated by regression analysis. Investigator and patient assessment of treatment response were compared between groups by X^2-tests.

Ethical aspects

The study was approved by the Danish Health Service and The local Ethical Committee and conducted according to the Helsinki Declaration II.

RESULTS

Thirty-four patients, 20 men and 14 women, aged 26–75 years (mean 43 years), were randomized into two groups. The calci-

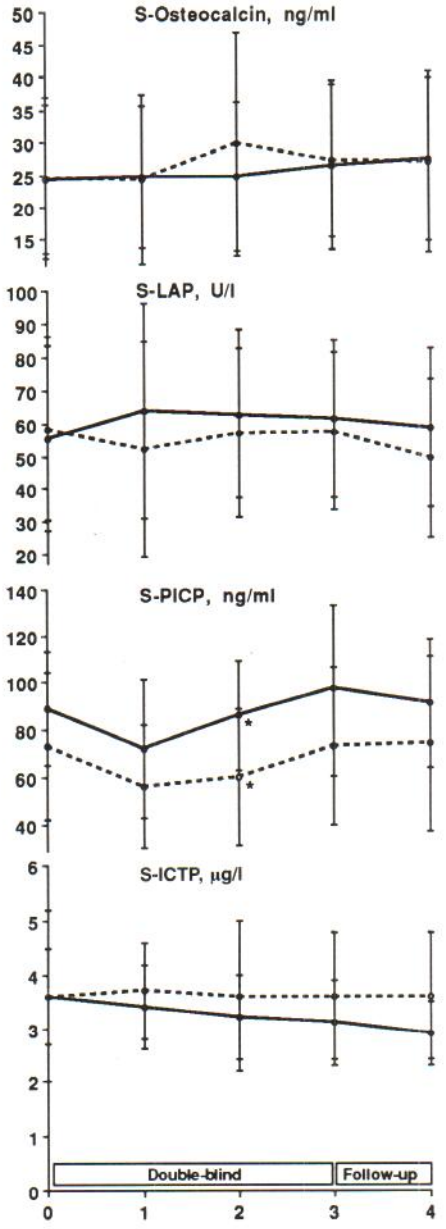

Fig. 2. Serum markers of bone metabolism (mean and SD). * = $p \leq 0.05$. (——) = Calcipotriol group, $n = 17$. (----) = Placebo group, $n = 17$.

potriol group ($n = 17$) and the placebo group ($n = 17$) were comparable at baseline visit with respect to age, extent of psoriatic affection, PASI score and level of biochemical parameters.

The mean weekly amount of calcipotriol ointment used was 40.3 g/week (range 8.2–94.4 g/week). Eleven patients used 0–50 g/week; 6 patients used 50–100 g/week. No correlation was found between the amount of ointment used and changes in any of the parameters of calcium and bone metabolism.

The PASI score (mean (SD)) at baseline visit was 12.33 (3.89) for the calcipotriol group and 11.99 (5.22) for the placebo group. During the 3-week study period of treatment, the PASI score for the calcipotriol group was reduced significantly more than for the placebo group ($p = 0.019$). The mean percentage reduction was 44.3% for the calcipotriol group versus 23.6% for the placebo group.

The serum-ionised calcium and 24-hour urine calcium remained constant in both groups during the period with no significant changes from baseline values or difference between groups. The values of S-PTH and serum-calcitonin did not change in either group during the study. There were no significant differences in mean between groups. Also, no significant changes were found in S-25-OH-D_3, which remained the same in the two groups.

A non-significant increase of serum-bone alkaline phosphatase was seen in the calcipotriol group. There were no significant changes in the serum-osteocalcin level, which remained nearly constant in both groups during the study. The baseline S-PICP was lower in the placebo group than in the calcipotriol group, whereas no difference was found between the groups in the S-ICTP. During the study S-PICP changed in both groups similarly; the only difference ($p<0.05$) found was at the visit of 2 weeks, most likely due to a difference in the initial levels. No significant changes were found in S-ICTP.

No calcipotriol was detected in any serum sample during the study.

DISCUSSION

The study showed no significant changes in markers of calcium and bone metabolism during topical treatment of psoriatic patients with calcipotriol (50 µg/g), max. 100 g/week, applied twice daily for 3 weeks. This calcipotriol dose was chosen because it was used without any change of serum-calcium in previous multicenter studies. In the present study, the examinations were validated by minimizing external influence on calcium and bone metabolism, by individual fixation of calcium intake, avoiding sun exposure and other treatment with effect on calcium or bone metabolism. If there was any effect of treatment with calcipotriol on markers of calcium and bone metabolism, the changes would be expected to occur within 3 weeks. Therefore treatment for 3 weeks should be adequate to observe any changes in these biochemical markers. Although it would have been of interest to monitor the patients treated for a longer period, it would have been difficult to do so in a controlled study.

The degree of clinical improvement was similar to that seen in previous studies with calcipotriol. During the study our patients had used the same amount of ointment as had the patients in the earlier clinical studies. The average patient had used about 50 g/week, which is about 50% of the max. permitted weekly consumption. The dose should be sufficient to show any short-term effects on calcium and bone metabolism. The results also support earlier studies (5–8) in showing no changes in serum-calcium level and the absence of changes in the more specific and sensitive markers of calcium and bone metabolism measured in this study. The calcium metabolism remained unchanged, with constancy in serum-calcium, serum-phosphate and urinary calcium excretion. The constancy in the calcium homeostasis was supported by the unchanged values of S-PTH and serum-calcitonin, both of which would have changed (decreased and increased, respectively) if there

been any calcitropic effect of the calcipotriol ointment. If there was an effect of topical calcipotriol on bone metabolism similar to the effect of vitamin D on bone metabolism, we should expect an increase in serum-bone-alkaline phosphatase and serum-osteocalcin, a decrease in S-PICP and an increase in S-ICTP. The markers of bone metabolism are very sensitive to changes and would change within the treatment period if calcipotriol ointment had had any effect on the homeostasis. There was no trend towards a change in this direction. Also S-25OH-vitD should decrease as a result of feed-back inhibition if calcipotriol had any calcitriol-like effect.

Recently, a study on the effect of calcipotriol on calcium metabolism was published (11). It was concluded that the study group receiving topical calcipotriol did not show any change in the measured parameters on calcium metabolism. However, the study did not have a placebo group, and apparently external factors, such as diet and sunlight exposure and medication, with effect on calcium or bone metabolism were not defined. Comparing this study with our own findings, we find the same calcium metabolic parameters unchanged, even though the patients in our study had used much more ointment (mean = 40.3 g/week) than in the other study (mean = 150 μg calcipotriol/day = 3 g ointment(50 μg/g)/day = 21 g/week).

The two case stories of patients developing hypercalcemia after use of calcipotriol ointment (7, 12) are not comparable to the patients in our study. Both had unstable psoriasis covering large areas of the body surface and they had used 200 or 400 g weekly, i.e. about 2–4 times the max. allowed weekly consumption. One of the patients had decreased renal function.

In conclusion, this study examined the effect of calcipotriol ointment on various biochemical markers of calcium and bone metabolism under calcium metabolic defined conditions and in amounts comparable to those used in previous clinical studies. Using the recommended dose, calcipotriol ointment 50 μg/g maximally 100 g/week for stable plaque-psoriasis in mild to moderate degree, we find no influence on calcium and bone metabolism.

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