

A Randomized Double-blind Comparison of the Effects on Systemic Calcium Homeostasis of Topical Calcitriol (3 µg/g) and Calcipotriol (50 µg/g) in the Treatment of Chronic Plaque Psoriasis Vulgaris

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Calcitriol and calcipotriol are effective treatments for psoriasis, although the two have never been directly compared. We compared the efficacy and toxicity of each agent in 24 patients with moderately extensive chronic plaque psoriasis, who were randomized in double-blind fashion to apply 90 g per week of either calcitriol (3 µg/g) ointment or calcipotriol (50 µg/g) ointment over an 8-week period. Mean PASI in patients applying calcitriol fell from 13 to 8.8 ($p < 0.05$) and in patients applying calcipotriol from 14.9 to 4.7 ($p < 0.005$). The reduction was significantly greater in the calcipotriol-treated group ($p < 0.05$). There was a small increase in serum ionized calcium in the calcipotriol-treated group (from 1.21 mmol/L to 1.25 mmol/L, $p < 0.05$) but no effect on calcium homeostasis in the calcitriol group.

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Several studies have indicated that both oral and topical calcitriol are effective in the treatment of chronic plaque psoriasis (1–7), although not all of these studies were assessed in double-blind fashion. Both oral and topical calcitriol have been shown to have significant effects on systemic calcium homeostasis when used in larger amounts. Topical calcipotriol has been extensively tested in the treatment of psoriasis (9–12) and has been shown to be effective and safe, although there have been occasional reports of adverse effects on systemic calcium homeostasis (11, 13, 14), even when the manufacturers' guidelines are adhered to (15). This study was designed to assess whether either agent, at a fixed dose, would have any effect on systemic calcium homeostasis. To facilitate the randomization and running of the study, Duphar Laboratories Ltd kindly allowed us to conduct the project in parallel with a multicentre study comparing the two agents.

MATERIALS AND METHODS

Male and female patients, aged 18–75 years, with moderately extensive psoriasis were asked to take part in the study. The study was approved by the Leicestershire Ethics Committee and full informed consent was obtained. Pregnant or breast-feeding females, patients receiving vitamin D, calcium supplements or any drug which might interfere with systemic calcium homeostasis, and patients who had received systemic anti-psoriatic therapy or UVB within the previous 4 weeks were excluded from the study. All other therapies for psoriasis were stopped during the study. Patients were randomized in double-blind

fashion to receive either topical calcipotriol (50 µg/g in white soft paraffin) or topical calcitriol (3 µg/g in white soft paraffin/liquid paraffin; 437.5 mg/562.5 mg). They were instructed to apply the ointment twice daily and to apply exactly 90 g per week (the ointments were dispensed in 90 g tubes). Patients were assessed at baseline and after 1, 2, 4, 6, and 8 weeks of therapy. Severity of psoriasis was assessed using the psoriasis area and severity index (PASI). Serum total adjusted calcium, ionized calcium, phosphate, alkaline phosphatase, parathyroid hormone (PTH), 25-hydroxyvitamin D, osteocalcin and 24 h urine calcium, phosphate, and hydroxyproline were measured at each visit.

Change in biochemical parameters was assessed by taking the average value on treatment for each patient and comparing with baseline using the paired *t*-test. Change in severity of psoriasis was assessed by comparing the PASI at baseline with PASI at week 8 (or at withdrawal), in each group, using the Wilcoxon signed rank test. The efficacy of the two agents was investigated by comparing the difference in PASI from baseline to week 8 (or withdrawal) in each group by means of the Mann Whitney U-test.

RESULTS

Twenty-four patients, 14 females and 10 males, were recruited. Twelve were assigned to the calcipotriol group, 12 to the calcitriol group. The groups were comparable at baseline in terms of biochemical parameters (Table I). There was no significant difference in the mean PASI of the two groups: calcipotriol group – 14.9 (SEM = 2.5), calcitriol group – 13 (1.0). Four patients in the calcipotriol group failed to complete 8 weeks' therapy. One of these was withdrawn after 6 weeks because of lack of efficacy, one after 4 weeks, because of the possibility of pregnancy. The other 2 failed to attend after 4, and 2 weeks' treatment. Four patients in the calcitriol group failed to complete 8 weeks' therapy. Two were withdrawn after 6 weeks because of lack of efficacy, one patient went abroad on holiday after 1 week of treatment and one failed to attend after the baseline visit. Baseline data were available on all patients, data from at least 4 visits on 21 patients and "on-treatment" data on all but one patient. Mean PASI in patients applying calcitriol fell by 32% from 13 to 8.8 ($p = 0.013$) and in patients applying calcipotriol by 68% from 14.9 to 4.7 ($p < 0.005$). The reduction was significantly greater in the calcipotriol-treated group ($p = 0.014$).

There was a small but significant increase in serum ionized calcium (Table I) in the calcipotriol-treated group (from 1.21 mmol/L to 1.25 mmol/L, $p = 0.01$) but no significant change in any of the other parameters of calcium homeostasis measured. There were no significant changes in any of the parameters measured in the calcitriol-treated group.

DISCUSSION

The use of vitamin D in the treatment of psoriasis was reawakened by the serendipitous observation of Morimoto &

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Table I. Serum and urine biochemistry at baseline and while on treatment for each agent. Figures indicate mean and in brackets SEM.

	Calcitriol		Calcipotriol	
	Baseline	On treatment	baseline	On treatment
Serum ionised calcium	1.20 (0.01)	1.22 (0.01)	1.21 (0.02)	1.25 (0.01)*
Serum total adjusted calcium	2.33 (0.02)	2.32 (0.03)	2.30 (0.02)	2.28 (0.02)
Serum phosphate	1.10 (0.07)	1.12 (0.05)	1.15 (0.07)	1.14 (0.05)
Serum alkaline phosphatase	72.3 (8.5)	75.5 (7.6)	71.0 (9.7)	78.2 (7.4)
Serum PTH	3.3 (0.3)	3.0 (0.2)	2.81 (0.38)	2.61 (0.21)
Serum 25-vitD	22.1 (4.6)	23.9 (3.1)	21.4 (3.3)	19.3 (2.5)
Serum osteocalcin	27.9 (3.6)	25.7 (4.1)	25.8 (2.9)	22.3 (3.3)
24 h urine calcium	4.03 (0.006)	3.96 (0.005)	3.95 (0.67)	4.38 (0.65)
24 h urine phosphate	21.1 (4.32)	24.1 (4.26)	21.17 (3.96)	28.27 (5.06)
24 h urine hydroxyproline	207.5 (30.3)	161.5 (31.1)	179.5 (25.9)	186.9 (25.3)

* $p=0.01$.

Kumahara (16) that oral 1-alpha vitamin D₃, for osteoporosis, improved a patient's psoriasis. Several studies (1-7) have since shown both oral and topical calcitriol to be effective, although not all of those trials were controlled. There were concerns about the potential toxicity of oral calcitriol in relation to systemic calcium homeostasis, and Holick et al. (17) found that oral doses of up to 2 µg induced hypercalciuria. If used in the long term, this could give rise to an increased risk of renal calculi. Toxicity from topical calcitriol has also been reported; hypercalciuria was detected in some patients using large amounts of topical calcitriol at a concentration of 15 µg/g (5, 6). The lower concentration of 3 µg/g has been reported to be safe in respect to calcium homeostasis and effective in the treatment of psoriasis, although patients only used relatively small amounts (6-8). For this reason, this concentration of calcitriol has been chosen for further development and will probably be marketed in the future for the treatment of psoriasis.

Because of the potential for toxicity of calcitriol, great efforts have been made to design and develop an analogue which has a weaker effect on systemic calcium homeostasis while retaining similar potency as an anti-psoriatic agent. Calcipotriol was the first analogue to be licensed for the treatment of psoriasis. It has been shown to be as potent as calcitriol in most respects, with the exception that it has less effect on systemic calcium homeostasis (18). This differential effect has been attributed to more rapid metabolism of calcipotriol, possibly mediated by reduced binding to vitamin D-binding protein in serum (19). Extensive clinical trials of calcipotriol in patients with psoriasis have shown no effect on systemic calcium homeostasis, provided that less than 100 g of the 50 µg/g preparation are used per week (9-12). However, most of the patients in these trials used much less than 100 g per week (average 30-40 g week), and in many studies only serum total adjusted calcium, a relatively insensitive index of systemic calcium homeostasis, was measured.

There have been reports of hypercalcaemia (11, 14) in patients using very large doses (up to 700 g per week), and we reported a rise in serum total adjusted calcium and 24 h urine calcium (20), and a fall in serum PTH (21) in patients using up to 300 g per week. We have also demonstrated a significant rise in 24 h urine calcium in 10 patients, using exactly 100 g per week of calcipotriol 50 µg/g (22), but no change in

serum total adjusted calcium. Serum ionized calcium was not measured.

The rise in serum ionized calcium in 12 patients in the current study suggests that topical calcipotriol may affect systemic calcium homeostasis when recommended doses are used. Although the change was small and of uncertain clinical significance, our results indicate that patients using doses approaching the maximum recommended should be monitored carefully. This is supported by a recent report of hypercalcaemia in 2 patients applying approximately 80 g per week (15).

It could be argued that we should have studied similar concentrations of calcitriol and calcipotriol. However, 3 µg/g is the concentration of calcitriol which is likely to be available commercially in the future, and 50 µg/g is the only concentration of calcipotriol available. We felt, therefore, that comparison of those preparations would be more clinically relevant.

This study confirms the efficacy of both topical calcitriol and calcipotriol in the treatment of chronic plaque psoriasis. Although calcipotriol was found to be significantly more effective, the concentration of calcitriol used (3 µg/g) was much lower than calcipotriol (50 µg/g). It may be worth investigating higher concentrations to determine whether it is possible to increase the therapeutic efficacy of calcitriol without adversely affecting systemic calcium homeostasis.

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