Psoriasis: Targets and Therapy

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ORIGINAL RESEARCH

Safety profiles of topical vitamin D_3 in psoriasis patients: a retrospective large-scale study

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Abstract: Topical vitamin D_3 ointments are widely used to treat psoriasis, sometimes in combination with cyclosporine, phototherapy, and biologic agents. However, the risk factors for hypercalcemia resulting from these ointments, and interactions with underlying disorders and age are unclear. We performed a retrospective study of psoriasis patients at Nagoya City University Hospital between January 1, 2004, and December 31, 2009, treated with a vitamin D_3-containing topical drug, either calcipotriol, maxacalcitol, or tacalcitol. Data from blood samples and clinical scores collected during routine visits throughout the study period were analyzed. We assessed changes in the serum calcium levels over time in association with age, liver dysfunction, renal dysfunction, concomitant medication, and concomitant therapy. Serum calcium levels were significantly lower in the calcipotriol group than in the maxacalcitol group ($P < 0.05$), regardless of other factors, at the observation period. Calcipotriol was associated with lower serum calcium levels than maxacalcitol in patients ≥ 65 years ($P < 0.05$), those with renal disease ($P = 0.0362$), and those with liver disease ($P = 0.0255$). Only three patients using calcipotriol developed hypercalcemia that did not seem to be related to the treatment. Hypercalcemia was observed in 10 patients using maxacalcitol, although serum calcium levels rapidly recovered when use was discontinued. Only one patient using tacalcitol developed hypercalcemia. Hypercalcemia tended to occur in patients with conditions in which the skin is more vulnerable, even at standard doses; patients taking oral etretinate; patients requiring concomitant systemic therapy, even if the Psoriasis Area and Severity Index score was not severe; and patients with renal or liver dysfunction. These findings highlight the importance of the awareness of the risk factors for hypercalcemia in patients treated with topical vitamin D_3 ointment, and point to calcipotriol as the first-choice treatment for those over 65 years old, or those with renal or liver disease.

Keywords: vitamin D_3, psoriasis, calcipotriol, maxacalcitol, tacalcitol, hypercalcemia

Introduction

Topical vitamin D_3 and topical steroids are first-line therapy for psoriasis. For second-line therapy, low-dose cyclosporine A and phototherapy are used.[1–3] The use of biologic agents for the treatment of severe psoriasis was recently approved and is also becoming more common. Topical agents containing vitamin D_3 are the basis for therapy for all levels of severity, and thus knowledge of the safe and appropriate use of these agents is extremely important for dermatologists. Adverse reactions to topical agents containing vitamin D_3 include local irritation at the application site and hypercalcemia. An understanding of the risk factors for hypercalcemia is critical.[4]

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Few studies of the risk factors of hypercalcemia have been published in Japan. In 2007, Miyachi et al[5] investigated the efficacy and safety of long-term topical treatment with calcipotriol ointment. Eleven patients with psoriasis vulgaris were observed over the course of 1 year, and with the small quantities of ointment that were used, there were no reports of hypercalcemia. Concomitant use of bath psoralen–ultraviolet (UV) A photochemotherapy (PUVA) therapy, but not retinoid or cyclosporine, was permitted during the course of this study.[5] Kono[6] presented an algorithm for the prevention of hypercalcemia after conducting a study of 20 Japanese patients with hypercalcemia who were using calcipotriol ointment. Stronger precautions were required with topical use of 90 g/week or more, when clear renal functional abnormalities and dehydration were observed, or when patients were taking calcium or vitamin D_3 supplements. Caution is also necessary in cases of pustular psoriasis, erythroderma, and concomitant use of cyclosporine and etretinate.[6]

In the present study, of 698 patients with psoriasis who were treated at Nagoya City University Hospital with a topical agent containing vitamin D_3, we performed a retrospective analysis on 264 patients who used an ointment containing high concentrations of calcipotriol, maxacalcitol, or tacalcitol alone. The agent used, age, concomitant therapy, concomitant medication, liver dysfunction, and renal dysfunction were then investigated as risk factors for hypercalcemia.

Subjects and methods

Subjects

Subjects comprised patients with psoriasis (including psoriasis vulgaris, pustular psoriasis, and psoriasis arthropica) who were treated at the Department of Dermatology of Nagoya City University Hospital between January 1, 2004, and December 31, 2009, with a topical agent containing vitamin D_3. During the study period, 1644 patients with psoriasis were treated at this department, of which 698 used a topical agent containing vitamin D_3 and could be analyzed. A total of 264 of these patients were being treated with an ointment containing high concentrations of calcipotriol, maxacalcitol, or tacalcitol alone, and these were the subjects analyzed in this study. There were 100 patients using calcipotriol, 107 patients using maxacalcitol, and 57 patients using tacalcitol. The mean application dose was 16.0 g/week for calcipotriol, 15.9 g/week for maxacalcitol, and 18.6 g/week for tacalcitol. The usage was similar. Topical steroid application was allowed in this study. The Ethics Committee of Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan, approved the study (#589).

Method

Retrospective analysis was conducted using regularly collected (once every 2 to 3 months) blood sample data and clinical scores during routine visits throughout the study period. Changes in serum calcium levels over time were assessed, and changes in serum calcium levels according to age, liver dysfunction, renal dysfunction, concomitant medication, and concomitant therapy were observed. The observations were conducted in stages (beginning at Stage 1), and regular blood sampling times during routine visits marked the times of these stages. Blood samples were routinely obtained every 2 to 3 months.

Observations conducted

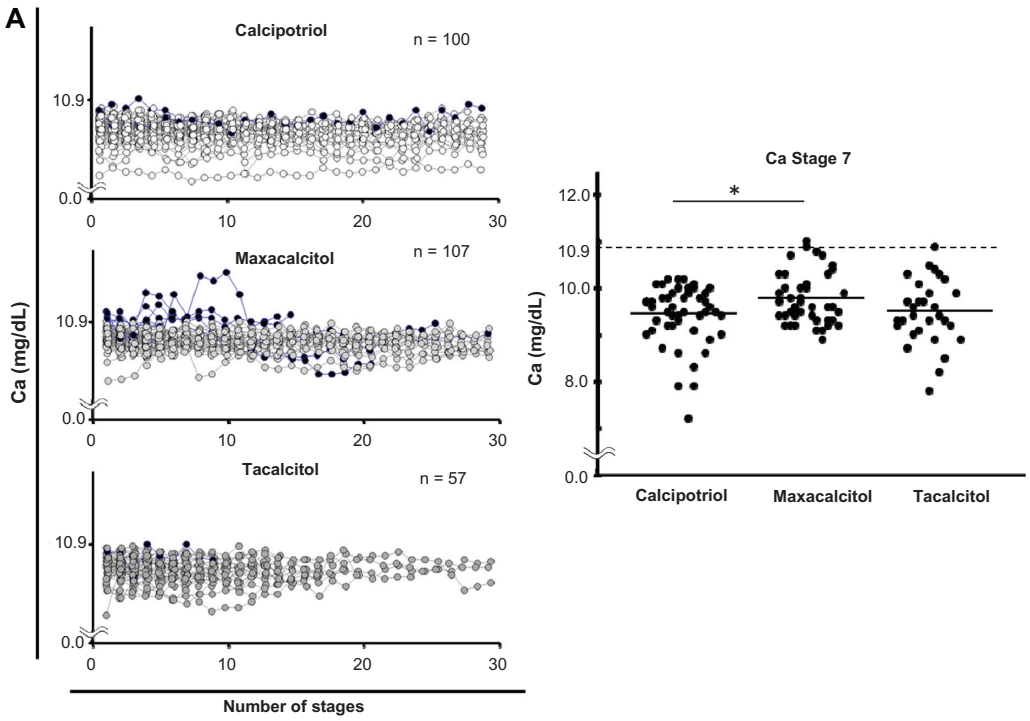
Serum calcium levels above the control group mean (Ca 10.9 mg/dL [mean +2 SD]) were considered to indicate hypercalcemia. Liver dysfunction was scored as "Yes (present)" when glutamic oxaloacetic transaminase (GOT), glutamic pyruvic transaminase (GPT) or γ-glutamyl transpeptidase (γGPT) levels above the upper limits (shown below) occurred during the study (upper limits: GOT 33 U/L, GPT 27 U/L, and γGPT 47 U/L). Serum creatinine levels of 1.0 mg/dL or higher during the course of observations were regarded as an indication of "Yes (present)" for renal dysfunction. If the patient was taking cyclosporine as concomitant medication, "Yes" was indicated for concomitant medication; otherwise, "No" was indicated. If the patient was taking PUVA therapy and phototherapy with narrow-band UVB as concomitant therapy, "Yes" was indicated for concomitant therapy; otherwise, "No" was indicated.

Statistical analysis

Pharmaco Analyst III (Three S Japan Co Ltd, Tokyo, Japan) (Student's *t*-test, Dunnett's test) was used to compare groups.

Results

Figure 1 shows the changes in serum calcium levels in each group according to the agent used. Serum calcium levels were significantly lower in the calcipotriol group (9.435 ± 0.089 mg/dL, $n = 51$) than in the maxacalcitol (9.747 ± 0.081 mg/dL, $n = 45$; $P < 0.05$) in Stage 7. Hypercalcemia developed in three patients in the calcipotriol group, 10 in the maxacalcitol group, and one in the tacalcitol group.



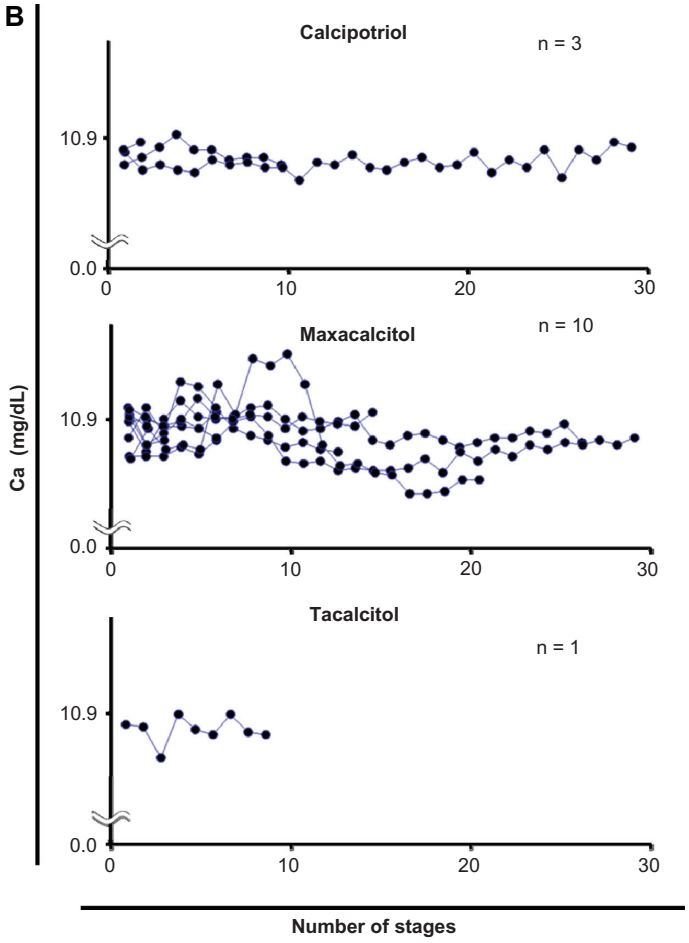


Figure 1 (**A**) Changes in serum calcium levels in all patients by agent used. • indicates patient with hypercalcemia. In Stage 7, serum calcium levels were significantly lower in the calcipotriol group than the maxacalcitol group. Dunnett's test was used for multiple comparisons of the other drugs with calcipotriol. (**B**) Patients with hypercalcemia only.

Among patients with liver disorder, serum calcium levels were significantly lower in the calcipotriol group than the maxacalcitol group (Figure 2). There were 67 patients with liver disorder in the calcipotriol group, 67 in the maxacalcitol group, and 40 in the tacalcitol group. In Stage 7, serum calcium levels were significantly lower in the calcipotriol group (9.426 ± 0.103 mg/dL, n = 43) than the maxacalcitol group (9.749 ± 0.091 mg/dL, n = 35; $P = 0.0255$). Hypercalcemia developed in some patients in each group during the course of observations: two in the calcipotriol group, eight in the maxacalcitol group, and one in the tacalcitol group. In all patient groups, there were no significant differences in serum calcium levels between patients with and without liver disorder.

Among patients with renal disorder, serum calcium levels were significantly lower in the calcipotriol group than in the maxacalcitol group (Figure 2). There were 15 patients with renal disorder in the calcipotriol group, six in the maxacalcitol group, and five in the tacalcitol group. In Stage 6, serum calcium levels were significantly lower in the calcipotriol group (9.390 ± 0.270 mg/dL, n = 10) than in the maxacalcitol group (10.550 ± 0.380 mg/dL, n = 4; $P = 0.0362$). Among these patients, there was one patient in the calcipotriol group, two in the maxacalcitol group, and one in the tacalcitol group that had hypercalcemia during the course of the observations. One patient from each of these groups (calcipotriol, maxacalcitol, and tacalcitol) had renal disorder in addition to liver disorder. In all patients, there were no significant differences in the serum calcium levels between patients with and without renal disorder.

Many patients in the calcipotriol group had high serum creatinine levels, but few had hypercalcemia. Figure 3 shows the changes in serum calcium levels in patients with renal disorder, as well as changes in serum creatinine levels in these

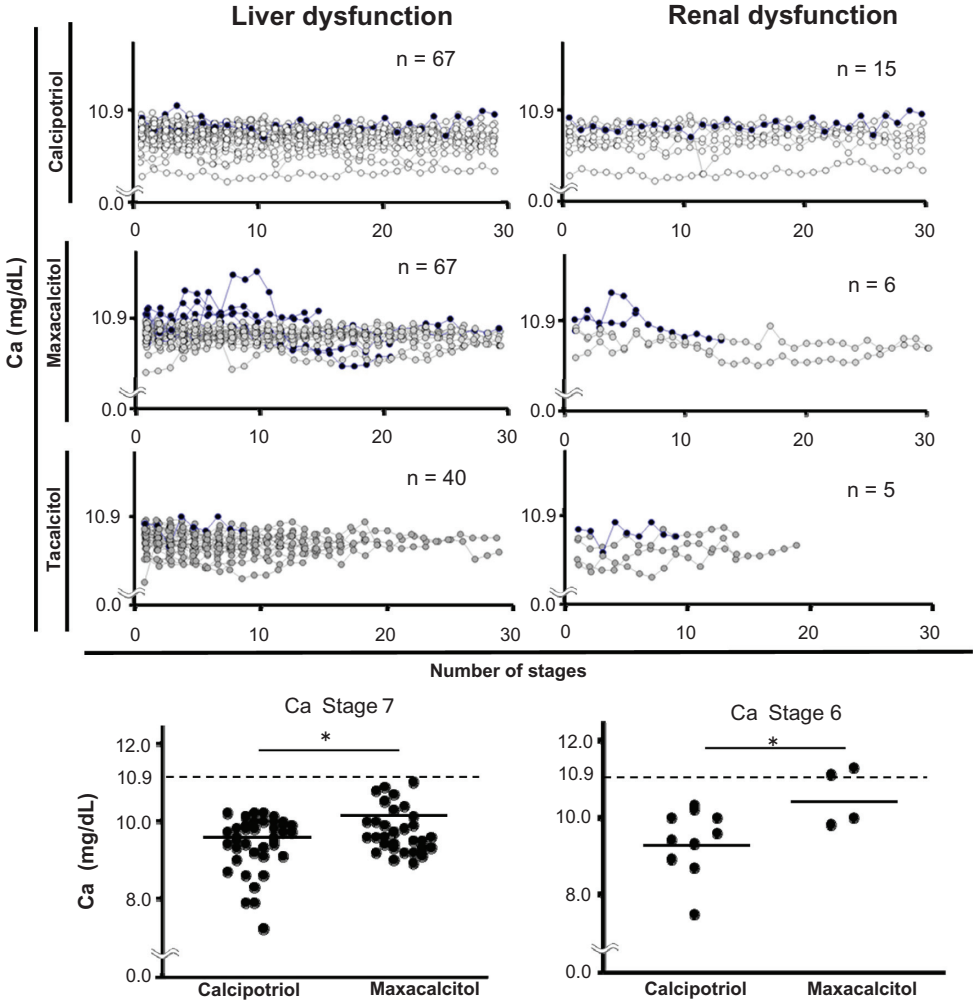


Figure 2 Changes in serum calcium levels in patients with liver disorder and renal disorder.
Notes: In Stage 7, serum calcium levels were significantly lower in the calcipotriol group than in the maxacalcitol group. In Stage 6, serum calcium levels were significantly lower in the calcipotriol group than in the maxacalcitol group. Student's *t*-test was used for a two-group comparison of calcipotriol and maxacalcitol.

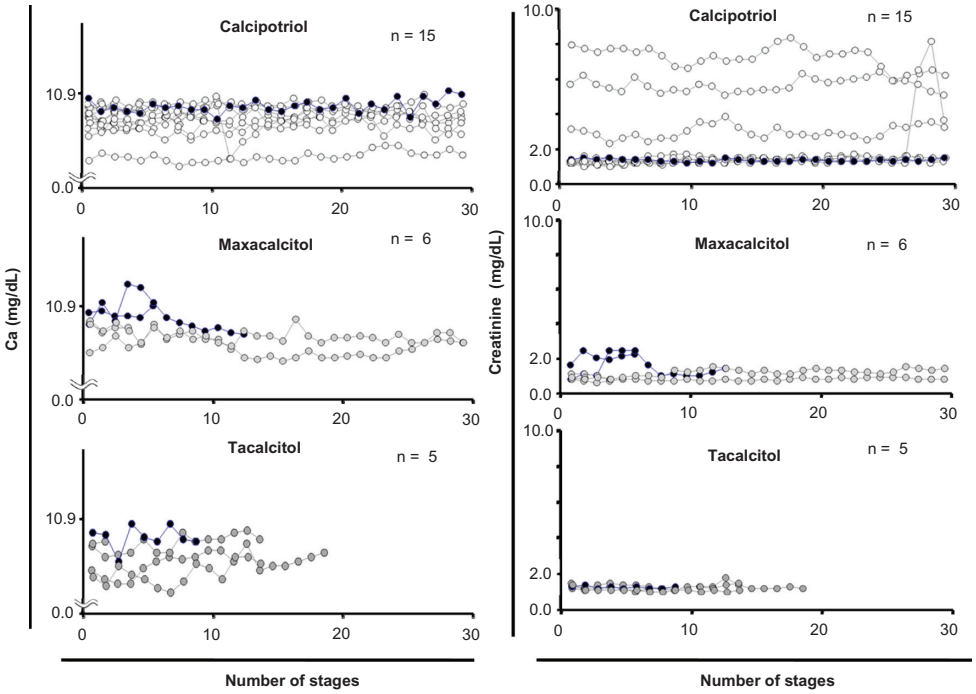


Figure 3 Changes in serum calcium/creatinine levels in patients with renal disorder by agent used.
Note: In the calcipotriol group, although patients with high serum creatinine levels are prominent, only one of these patients had hypercalcemia.

patients. In the calcipotriol group, there were more patients with renal disorder (15 patients) than in other groups (six maxacalcitol patients) (five tacalcitol patients), and patients with high serum creatinine levels were also prominent. Only one patient with hypercalcemia had a single kidney following surgery for renal cell carcinoma, and during the course of observations presented serum creatinine levels of 0.8 to 1.3 mg/dL, irrespective of dermatologic symptoms of psoriasis or the ointment dose, accompanied by changes in serum calcium levels. Two hypercalcemic patients in the maxacalcitol group showed both elevated serum calcium and creatinine levels, which improved in each case after discontinuation of maxacalcitol ointment. One patient was elderly (85 years old) and died during the course of observations due to cerebral hemorrhage. One patient in the tacalcitol group with hypercalcemia underwent treatment involving topical application of a dose of 80 to 130 g/month and hospitalization for PUVA therapy due to a Psoriasis Area and Severity Index (PASI) score of 14, and subsequently developed hypercalcemia. As the lesions improved, the topical dose was reduced (30–50 g/month), and serum calcium levels dropped as a result.

In patients aged ≥ 65 years with concomitant phototherapy, liver disorder, or concomitant phototherapy and liver disorder, serum calcium levels were significantly lower in the calcipotriol group than in the maxacalcitol or tacalcitol groups (Table 1). Table 1 shows the comparison of serum calcium levels with the three vitamin D_3 topical agents, divided

Table 1 Comparison of serum calcium levels with three topical vitamin D_3 agents, divided between patients aged ≥ 65 years and patients < 65 years

Age (year-old)	Phototherapy	Hepatopathy	Nephropathy	n			Dunnett's ※ ($P < 0.05$)
				Calcipotriol	Maxacalcitol	Tacalcitol	
≥65	○			6	8	10	C < M < T ※
		○		19	18	17	C < M ※
	○	○		5	5	10	C < M < T ※
<65	○			10	9	6	NS
		○		24	17	8	NS
	○	○		10	7	4	NS

Notes: In patients aged ≥ 65 years, with concomitant phototherapy, liver disorder, or concomitant phototherapy and liver disorder, serum calcium levels were significantly lower in the calcipotriol group than in the maxacalcitol or tacalcitol groups.

between patients aged ≥ 65 years and those <65 years. In patients < 65 years, there were no significant differences in the serum calcium levels, regardless of the topical agent used, and irrespective of the presence or absence of comorbidities or concomitant phototherapy. In those aged ≥ 65 years with concomitant phototherapy, liver disorder, or concomitant phototherapy and liver disorder, serum calcium levels were significantly lower in the calcipotriol group than in the maxacalcitol or tacalcitol groups. No significant differences in serum calcium levels were observed, regardless of the presence or absence of renal disorder.

Discussion

There are several reports on calcipotriol ointment and hypercalcemia, and case reports on overdosing appear frequently.[4,7,8] Cases of hypercalcemia due to the consumption of calcium lactate and milk in addition to topical application of calcipotriol ointment have also been reported,[9] and hypercalcemia can occur in cases of widespread erythrodermic psoriasis, even at topical doses of less than 100 g/week.[10,11] Bleiker et al[12] reported hypercalcemia in five of 28 patients with severe psoriasis receiving high-dose topical calcipotriol (200–360 g/week) over a 6-month observation period. During their observation, with the exception of topical application of steroids/dithranol, no concomitant systemic therapy, such as phototherapy, was administered. In addition, Bourke et al[13] observed hypercalcemia in five of 16 patients with topical application of up to 360 g/week for 2 weeks, and reported topical dose-dependent increases in serum calcium levels. On the other hand, Poyner et al[14] reported no hypercalcemia, renal disorders, or liver disorders in 203 psoriasis patients over the course of 48 weeks of observations in a multicenter open-label study, in which the average dose for the 6 weeks was 16.5 g/week, followed by a gradual reduction in topical dose thereafter. There was no concomitant systemic therapy, and patients with liver disorders or renal disorders were excluded, as were patients with active psoriasis. Klaber et al[15] reported no hypercalcemia in 167 psoriasis patients using up to 100 g/week, with topical therapy continuing for 1 year. In addition, Kragballe et al[16] reported no hypercalcemia in 15 patients with plaque-type psoriasis, with the use of up to 100 g/week for 6 months. Together, the findings of these previous reports suggest the following risk factors for hypercalcemia: calcipotriol ointment use at high doses, concomitant use of other vitamin preparations, and patients with psoriasis with widespread lesions.

In the present study, we investigated hypercalcemia occurrences in 698 psoriasis patients being treated with topical vitamin D_3 application, according to age, presence or absence of concomitant phototherapy, presence or absence of oral cyclosporine use, and presence or absence of liver disorders and renal disorders. These factors were also investigated by preparation, as there have been few previous reports on hypercalcemia from topical vitamin D_3 application in patients with liver disorders or renal disorders. During the course of our study, hypercalcemia was observed in 14 of 698 patients; three patients used calcipotriol ointment, 10 patients used maxacalcitol ointment, and one patient used tacalcitol ointment.

Of the three patients using calcipotriol ointment who had hypercalcemia, two had underlying conditions; one patient had a solitary kidney after surgery for renal cell carcinoma, and another had a floating kidney and had experienced hypercalcemia prior to calcipotriol ointment use, but this did not get worse with topical use. The one patient without an underlying condition was a 46-year-old woman with plaque-type psoriasis, whose rash rapidly improved to a clear PASI score using 20 to 50 g/week. There were variations in serum calcium levels unrelated to topical use, and a relationship to topical use is considered unlikely.

Hypercalcemia was observed in 10 patients on maxacalcitol. In these patients, serum calcium levels rapidly normalized when topical use was discontinued or the dose was reduced, and hypercalcemia is believed to have been caused by the topical application. One patient was a 78-year-old man with renal disorders, hepatitis C, prostate cancer, and a history of cerebral infarction, with a psoriasis PASI score of 6.3, undergoing concomitant phototherapy. The topical dose was not high at 20 to 25 g/week. The second patient was a 55-year-old man with a history of alcoholic cirrhosis and widespread psoriasis with a PASI of 26. The topical dose was in the standard range (50 g/week). The third patient was a 35-year-old man with psoriasis and liver disorders on concomitant oral etretinate. The dose was 25 to 50 g/week. In the first two patients, serum calcium levels normalized when topical use of maxacalcitol ointment was discontinued; in the third patient, serum calcium levels normalized when the topical dose was reduced to 18 to 25 g/week.

The patient using tacalcitol ointment who had hypercalcemia was a 62-year-old man with renal disorder and moderate psoriasis with a PASI score of 14.2, who was undergoing concomitant PUVA therapy. The topical dose was not high (33 g/week). As the lesion improved, the topical dose was reduced to about 10 g/week, and serum calcium levels decreased.

Based on analysis of these cases, hypercalcemia tends to occur in patients with coexistent systemic conditions in which the skin becomes vulnerable, such as hepatitis and hepatic cirrhosis, even when the dose was within the standard range; patients taking oral etretinate; patients requiring concomitant systemic therapy, even if the PASI score was not severe; and patients with renal disorders.

Serum calcium levels were significantly lower in the calcipotriol group than in the maxacalcitol group, and the results were similar in patients with liver disorders and in patients with renal disorders. Thus, the use of calcipotriol ointment in patients with liver dysfunction or renal dysfunction is considered to be safer with respect to the adverse reaction of hypercalcemia. In addition, despite the fact that among patients with renal disorders, there were more patients with high serum creatinine levels in the group of patients taking calcipotriol than those taking maxacalcitol and tacalcitol, calcipotriol could be selected for patients with renal disorders. In patients aged ≥ 65 years, serum calcium levels were significantly lower in the calcipotriol group among patients undergoing concomitant phototherapy, in patients with liver disorders, and in patients with liver disorders undergoing concomitant phototherapy; and although statistical analyses that included PASI scores were not possible in the present study, calcipotriol ointment should be the topical agent selected for elderly patients with liver disorders, and for those with psoriasis with comparatively widespread or intractable lesions who require phototherapy. Statistically, based on examination of the patients who developed hypercalcemia, there were no findings indicating that concomitant cyclosporine should be considered a risk factor. At our hospital, most cases are controlled through the use of low-dose cyclosporine, and changing to other therapies is considered in patients with uncontrollable lesions. Consequently, in psoriasis patients who can be controlled by low-dose oral cyclosporine, the topical dose is considered to be small, and therefore, will probably not become a risk factor in these cases.

The present findings together with data from previous reports highlight the need for awareness concerning the risk of hypercalcemia when topical vitamin D_3 agents over the standard dosage are used, and in patients with kidney disorders or with severe psoriasis, such as erythrodermic psoriasis. Based on the results of the present study, even at less than half the standard dose, there is a risk of hypercalcemia if oral etretinate is used, as well as in cases complicated by liver disease in which the skin becomes vulnerable. Caution should be used in selecting the vitamin D_3 topical agent for patients with early-stage renal disorders, even when serum creatinine levels are not high (≥1.0 mg/dL), as the risk of hypercalcemia decreases in patients using calcipotriol ointment. Similarly, it is necessary to exercise caution in patients aged ≥ 65 years with liver disorders, and with relatively widespread and intractable symptoms, such as those that require concomitant phototherapy.

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Disclosure

The authors report no conflicts of interest in this work.

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